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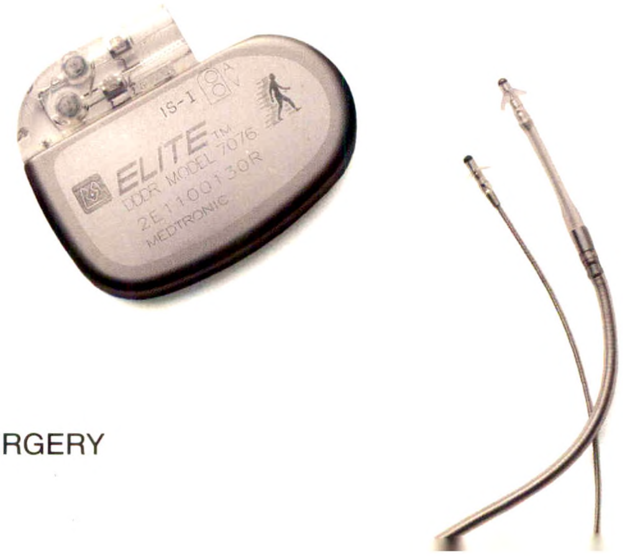

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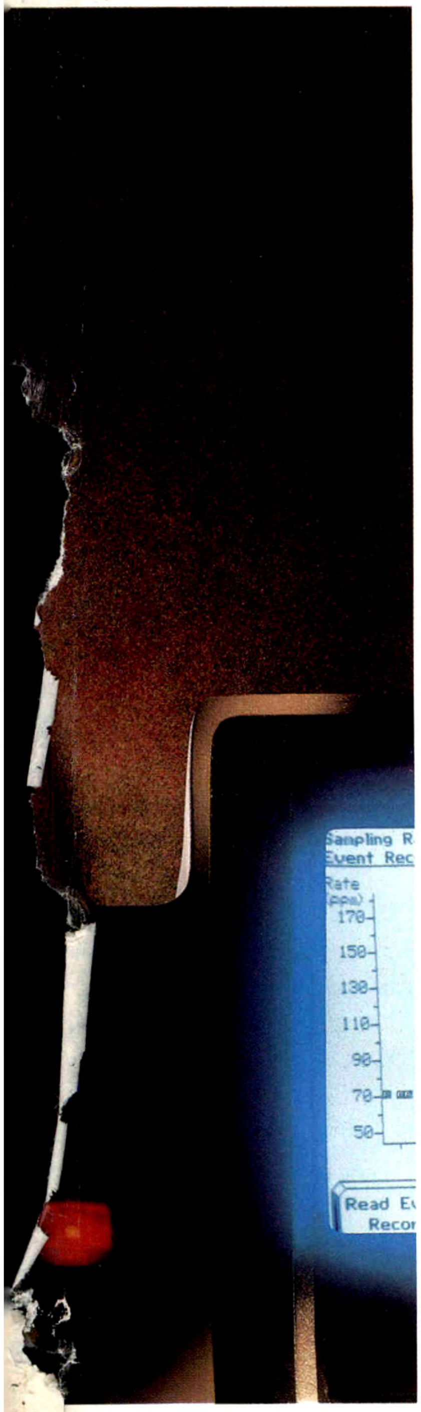

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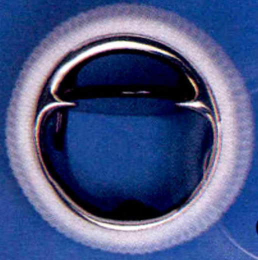

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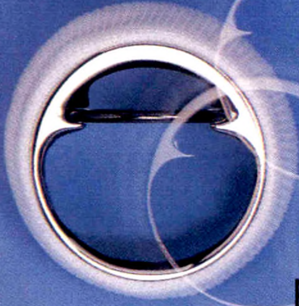

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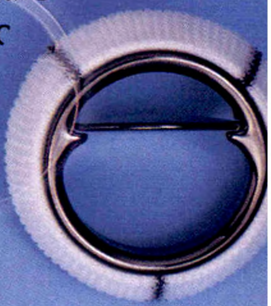

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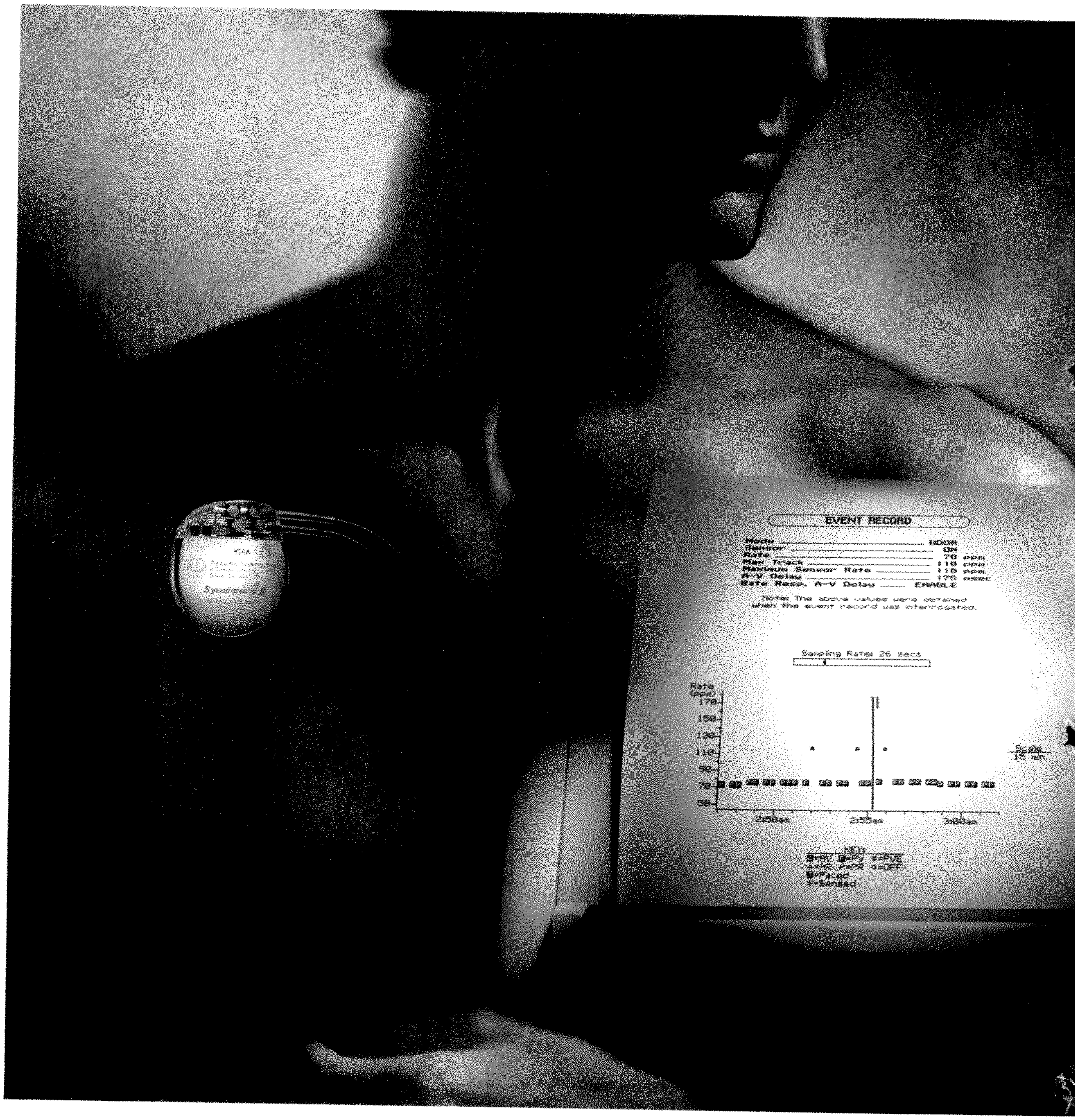

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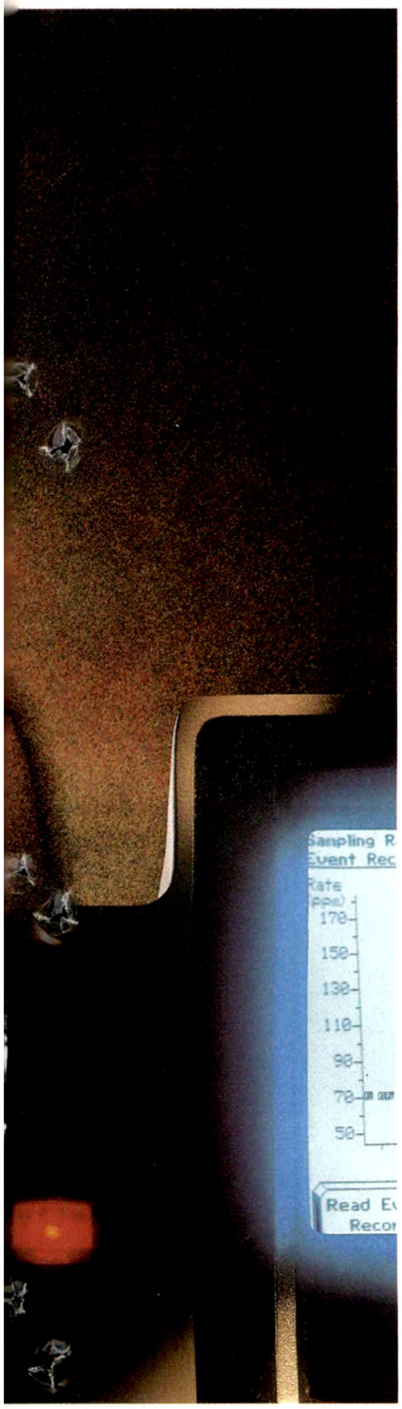

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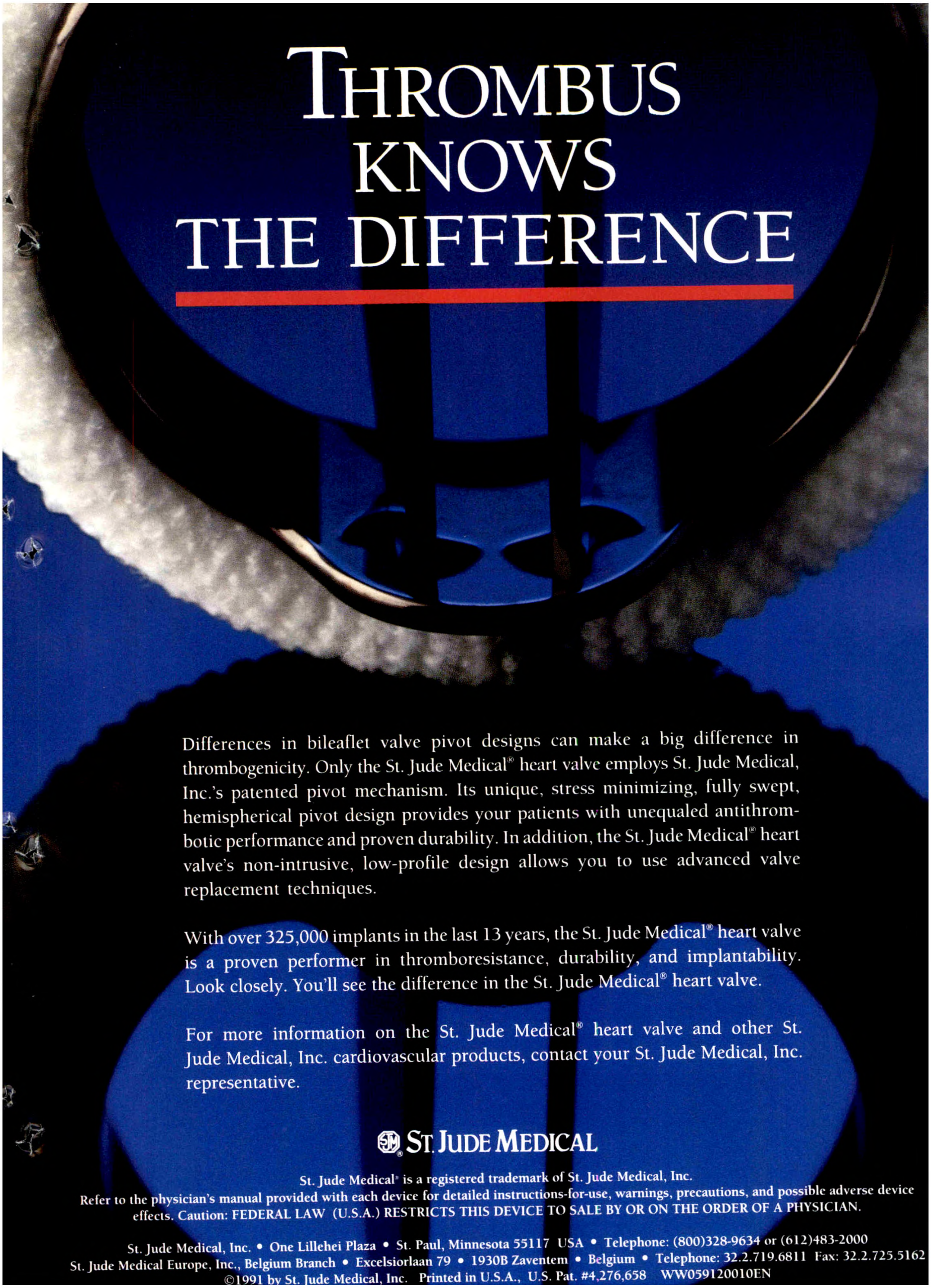

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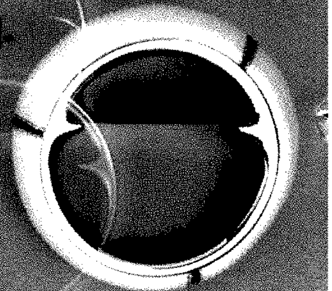

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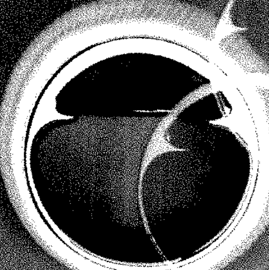

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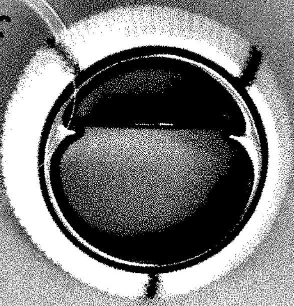

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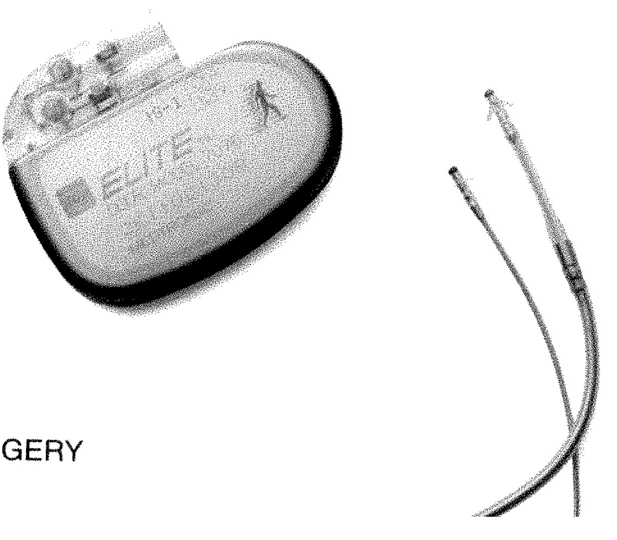

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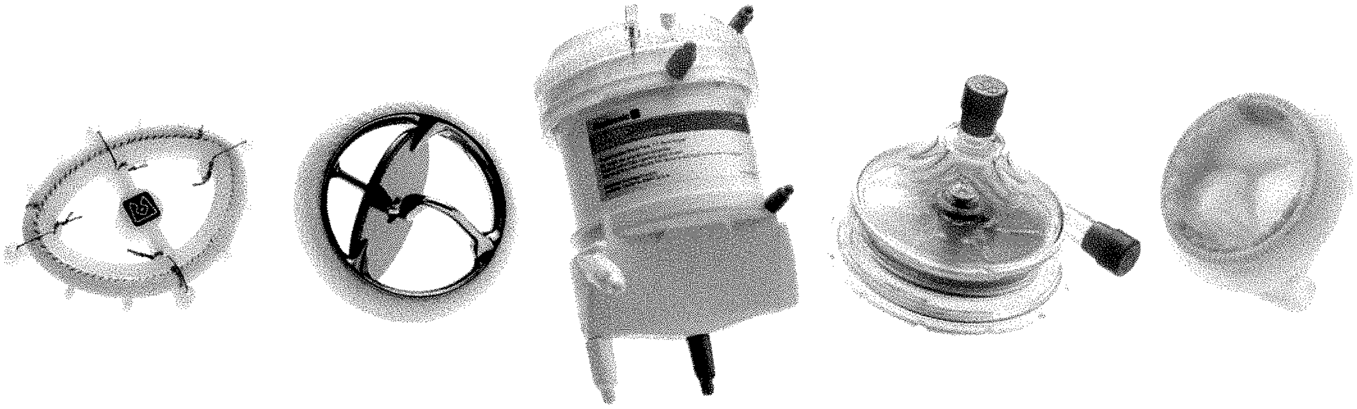

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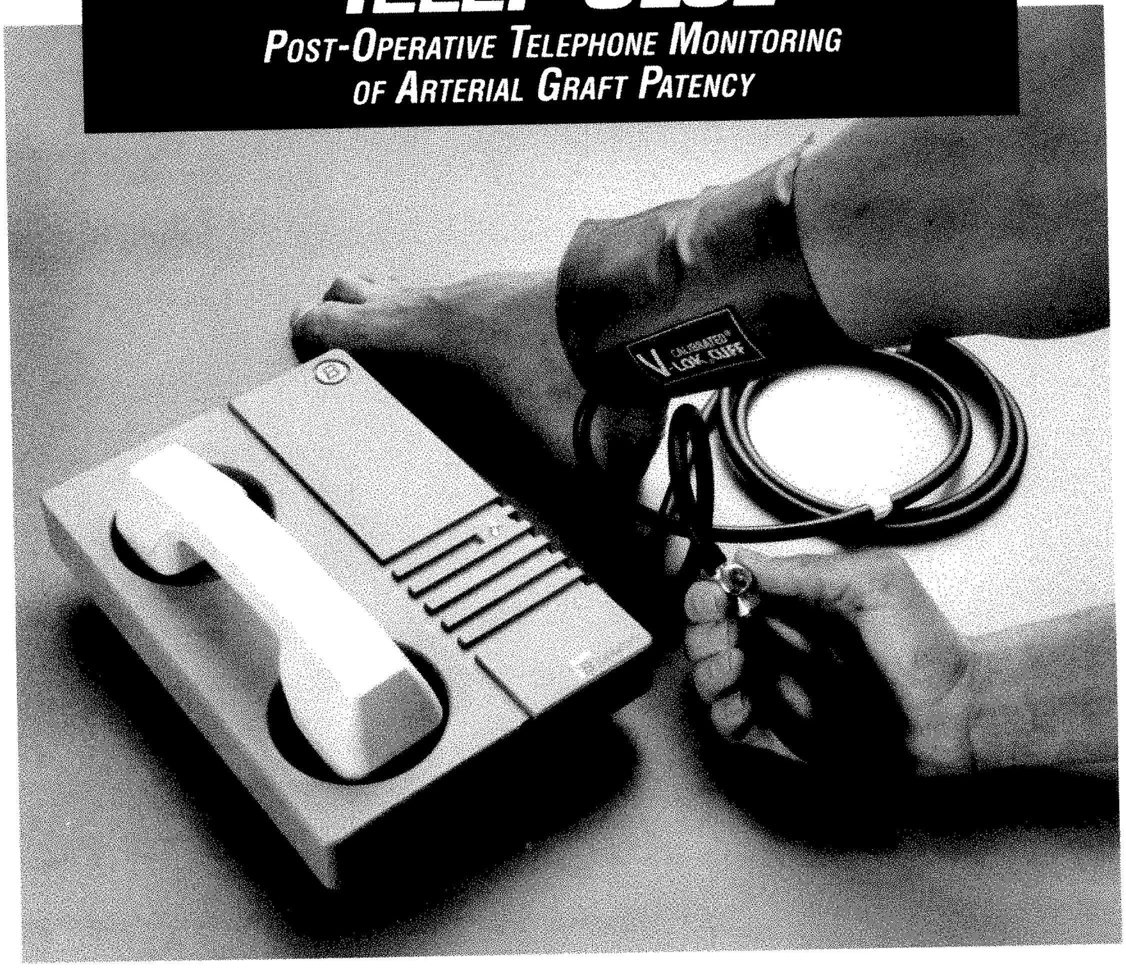

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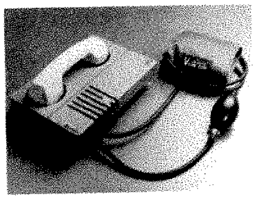

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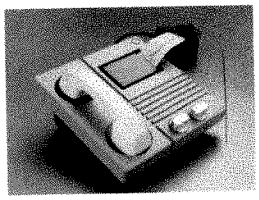

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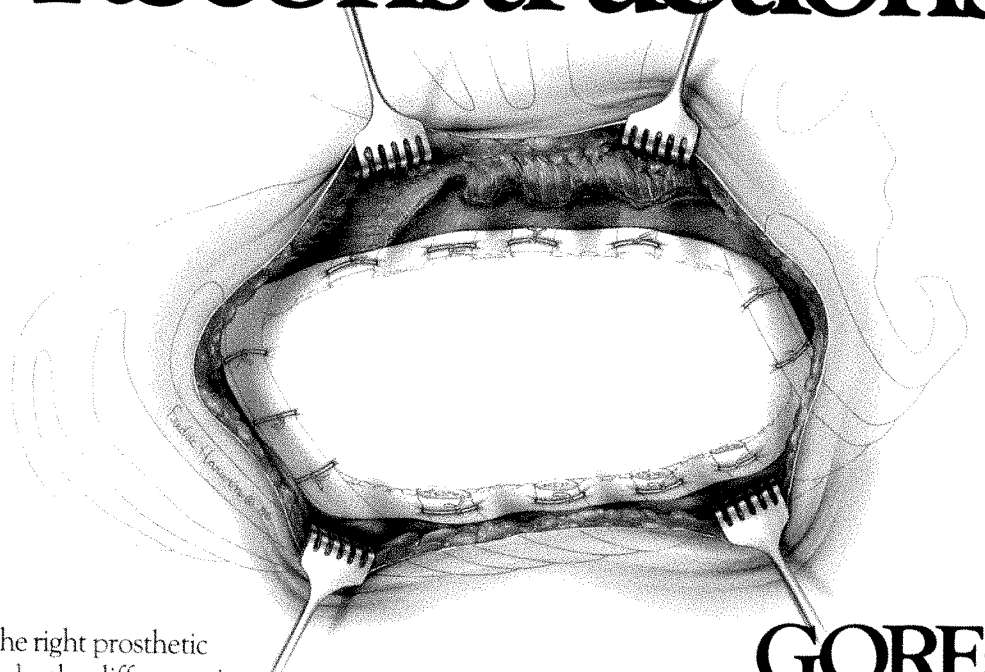

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The porcine aortic valves are fixed in buffered glutaraldehyde, and then mounted on cloth-covered frames. After mounting, the valves are tested *in vitro* to ascertain their competency and flow characteristics. After final inspection, the valves are sterilized, rinsed, and then transferred into fresh glutaraldehyde and packaged under aseptic conditions.

Low Pressure Fixation

In vitro studies by Broom, et al., advise that to maintain optimum mechanical properties in the fixed porcine aortic leaflet tissue, the full collagen waveform or crimp originally present in the relaxed fresh tissue should be retained. In addition, these studies show that the collagen waveform is sensitive to alteration at fixation pressures as low as 4 mm Hg. Edwards CVS Division has developed a process to fix porcine aortic valves at a hydrostatic pressure less than 4 mm Hg to minimize alterations in the collagen waveform of the aortic valve tissue. Low pressure fixation of Carpentier-Edwards Duraflex™ bioprostheses is intended to increase the clinical durability of these valves; however, data regarding Carpentier-Edwards Duraflex™ bioprostheses are insufficient to demonstrate that durability has been increased by this preparation technique or that calcification has been reduced.

Indications

Bioprostheses are indicated for use in patients suffering from valvular heart disease. Mitral valvular heart disease is a condition involving any of the following: obstruction of the heart valve or stenosis; leakage of the valve, known as regurgitation or insufficiency; and combination of the two, sometimes referred to as mixed disease or combined lesions.

Valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various microorganisms, degenerative calcification, rheumatic heart disease, and rupture or dysfunction of the mitral subvalvular mechanism secondary to myocardial ischemia.

Bioprostheses are used particularly in those patients for whom long-term anticoagulation is contraindicated or who may be difficult to maintain on anticoagulation therapy.

The Carpentier-Edwards Duraflex™ bioprosthesis is intended for use in patients whose mitral valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one. It is also intended for use in patients with a previously implanted mitral valve prosthesis which is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis.

Warnings
For Single Patient Use Only

In the presence of conditions affecting calcium metabolism or when calcium containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, and in patients who are on maintenance hemodialysis.

The decision to use a tissue valve must ultimately be made by the physician on an individual basis after carefully evaluating the short- and long-term risks and benefits to the patient, and considering alternative methods of treatment. The overall durability, especially long-term, has not been established for bioprostheses.

Serious complications, sometimes leading to replacement of the valve and/or death, may be associated with the use of tissue valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery.

Note: Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis (See Clinical Experience).

Careful and continuous medical follow-up (at least annually by a visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed.

Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection.

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall or history of previous atrial thrombosis. Please refer to the most recent Clinical Experience attachment for data on anticoagulation relating to these valves. The appropriate anticoagulation therapy must be determined by the physician on an individual basis.

Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc. should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

Carpentier-Edwards Duraflex™ bioprostheses must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.

Passing diagnostic catheters and transvenous pacing leads across Carpentier-Edwards* Duraflex™ bioprostheses could damage the valve. Consequently, it is recommended that these procedures be avoided.

Both the valve and glutaraldehyde storage solution are sterile. The outside of the jar is not sterile and must not be placed in a sterile field. Furthermore, the valve and container should never be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation.

Storage between 10° C (50° F) and 25° C (77° F) is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue.

Glutaraldehyde may cause irritation of the skin, eyes, nose and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact with the eyes, seek medical attention.

Surgical Precautions

The models 6625LP and 6625-ESR-LP Duraflex™ mitral valves are unapproved for indications other than mitral valve replacement.

Complications

As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device.

Complications associated with the use of Carpentier-Edwards Duraflex™ bioprostheses, compiled from the literature and from reports received through the complaint handling system in accordance with the United States (federal) regulations establishing Good Manufacturing Practices section 820.198, include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding related to the use of anticoagulant therapy, ventricular perforation by stent posts, looped sutures, and malfunctions of the valve due to distortion at implant or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, suture abrasion, instrument trauma, and leaflet or aortic wall detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrhythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct.

Note: Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes a potential relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period, and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards Duraflex™ bioprostheses to calcification as compared to other commercially available porcine valves.

See package insert accompanying product for a full discussion of warnings, contraindications, complications and prescribing information.

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

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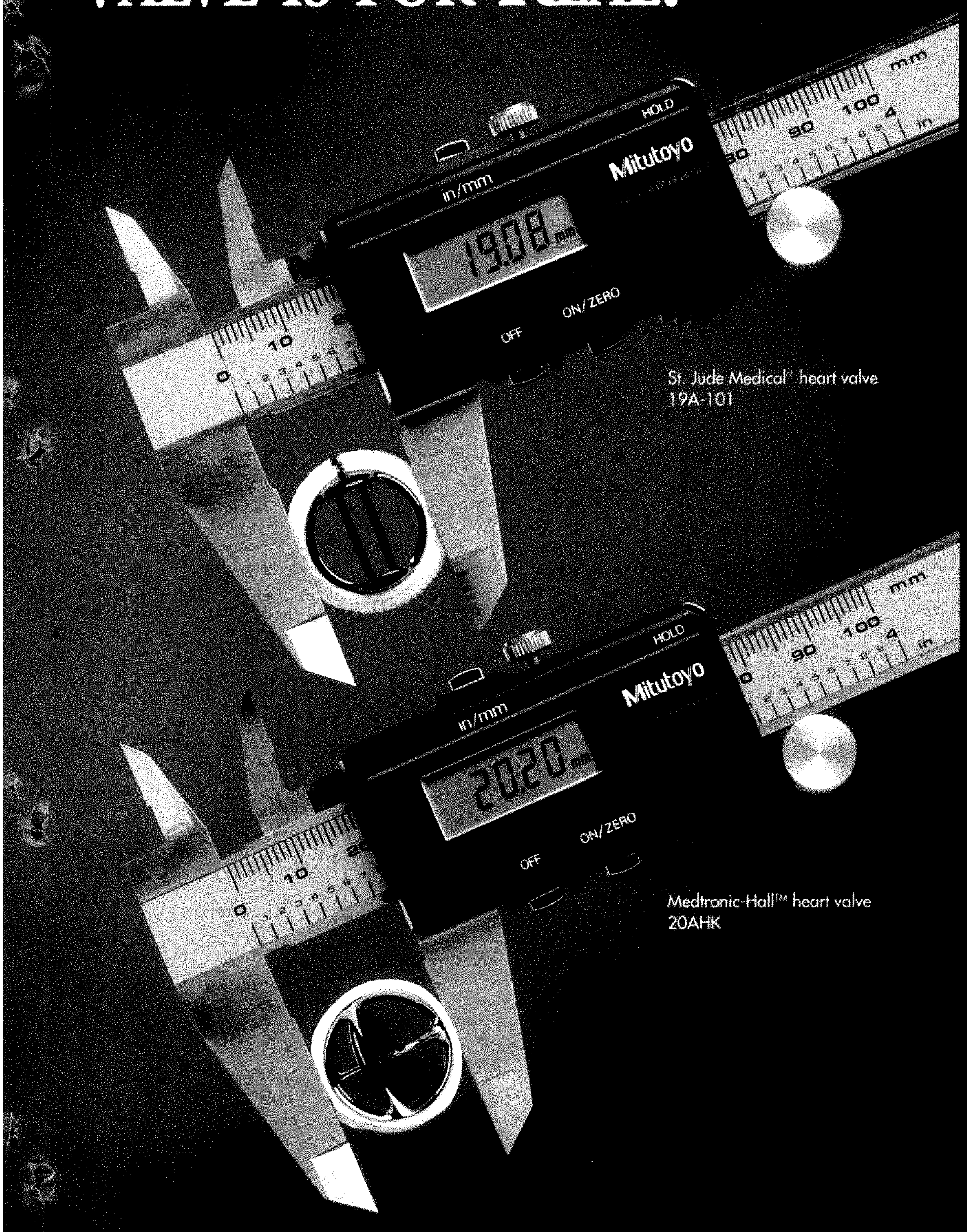

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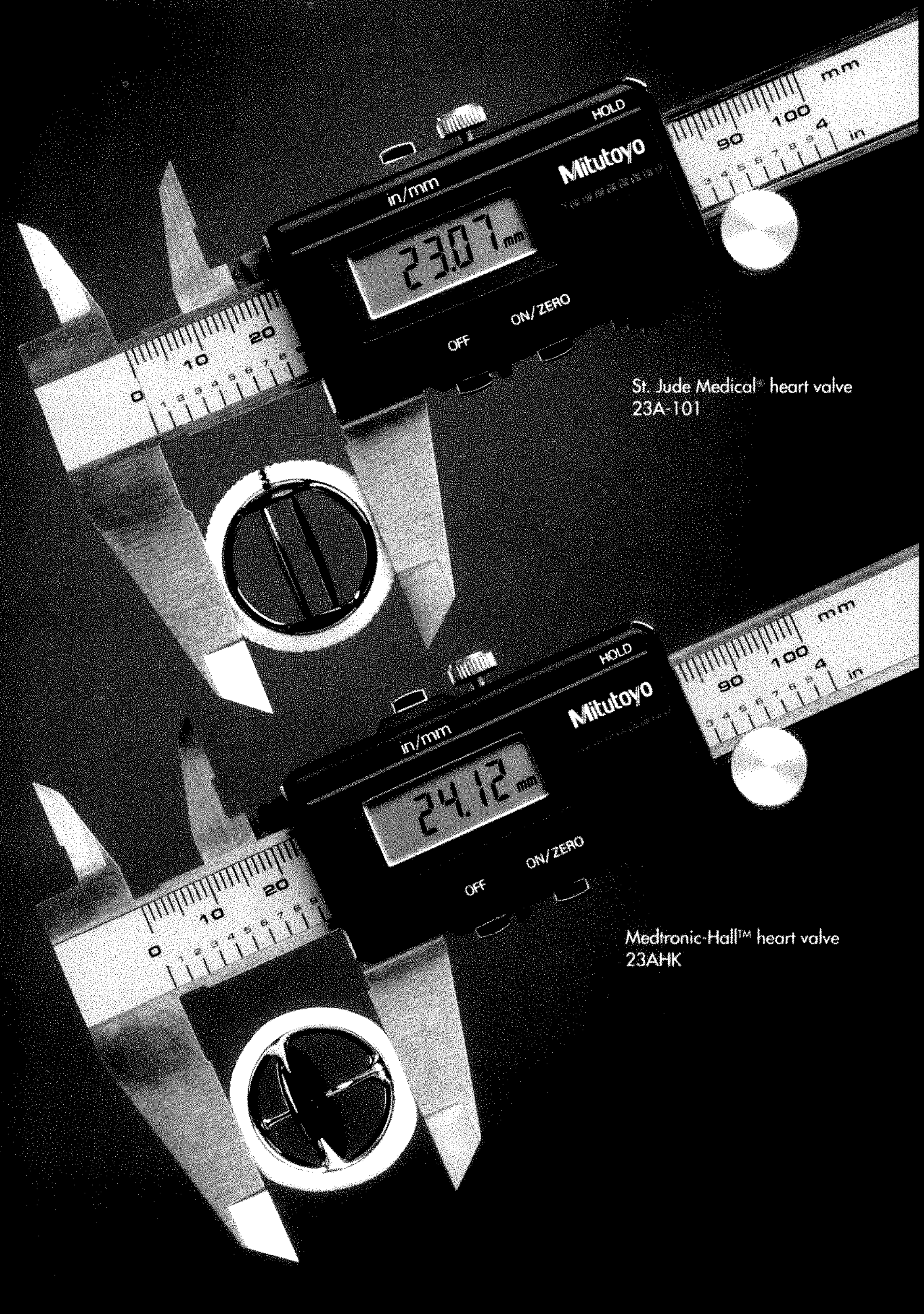

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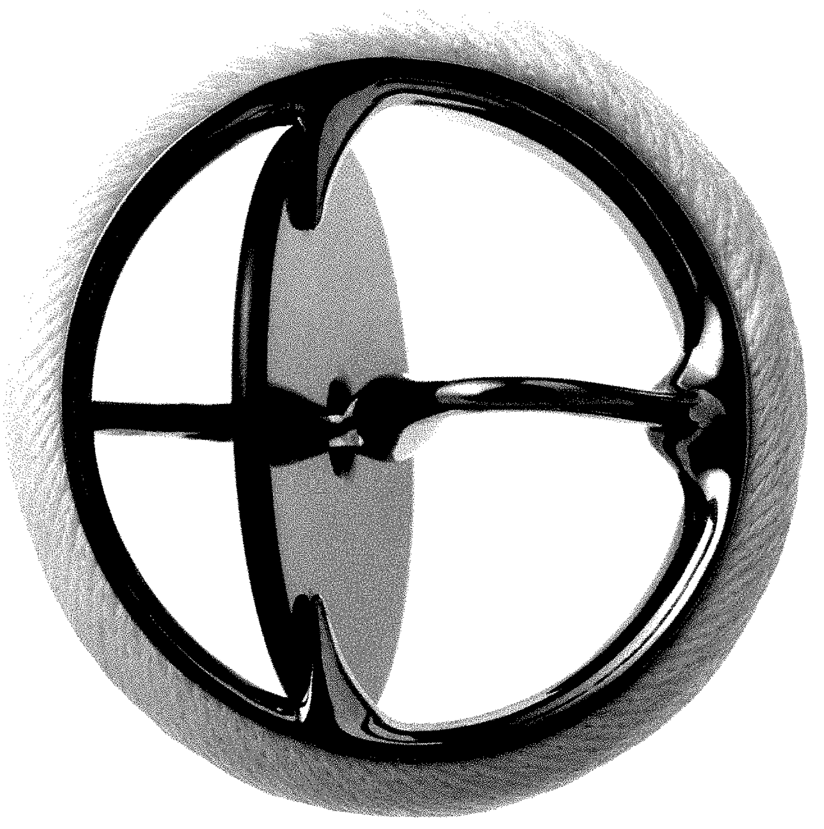

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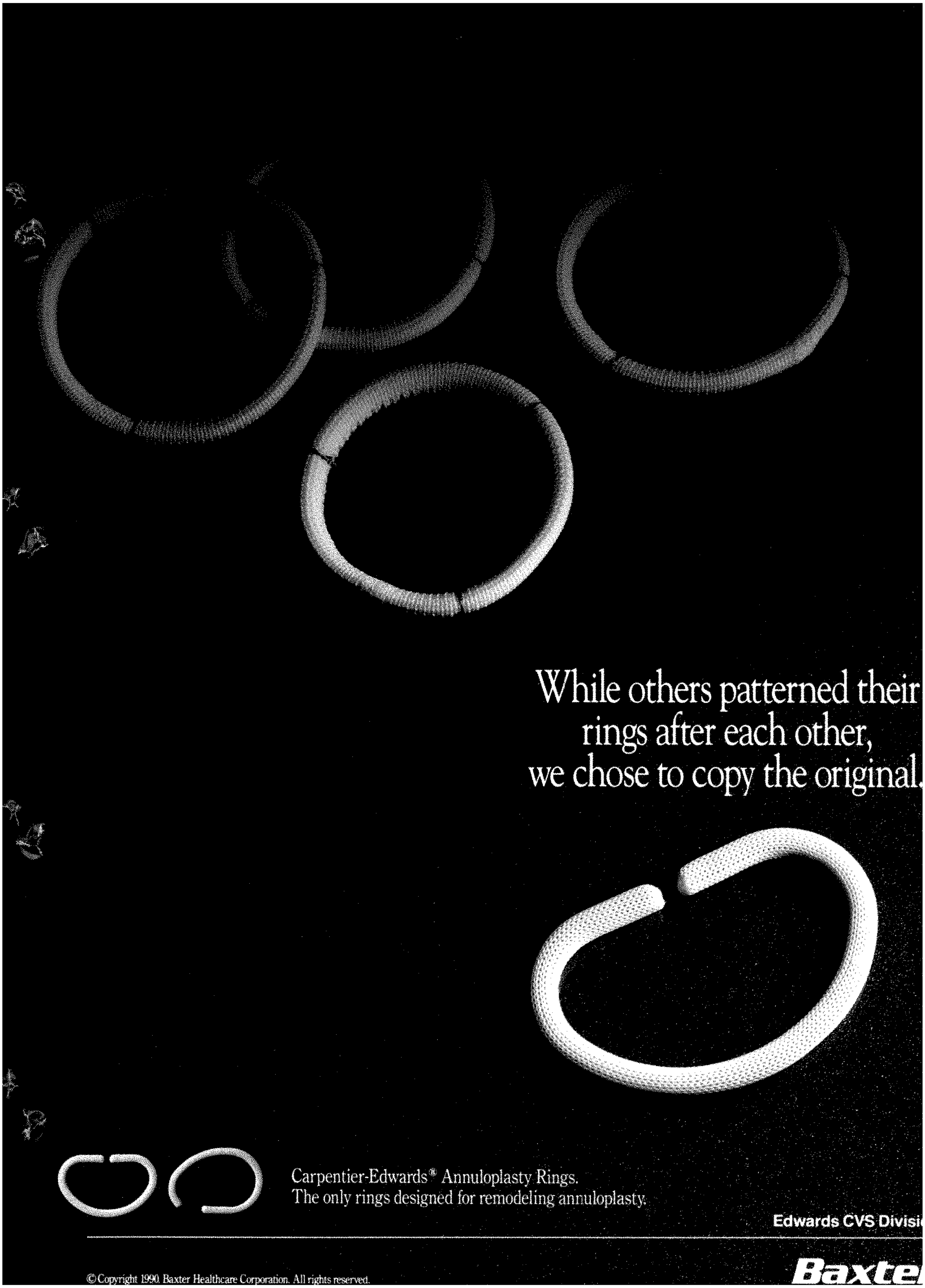

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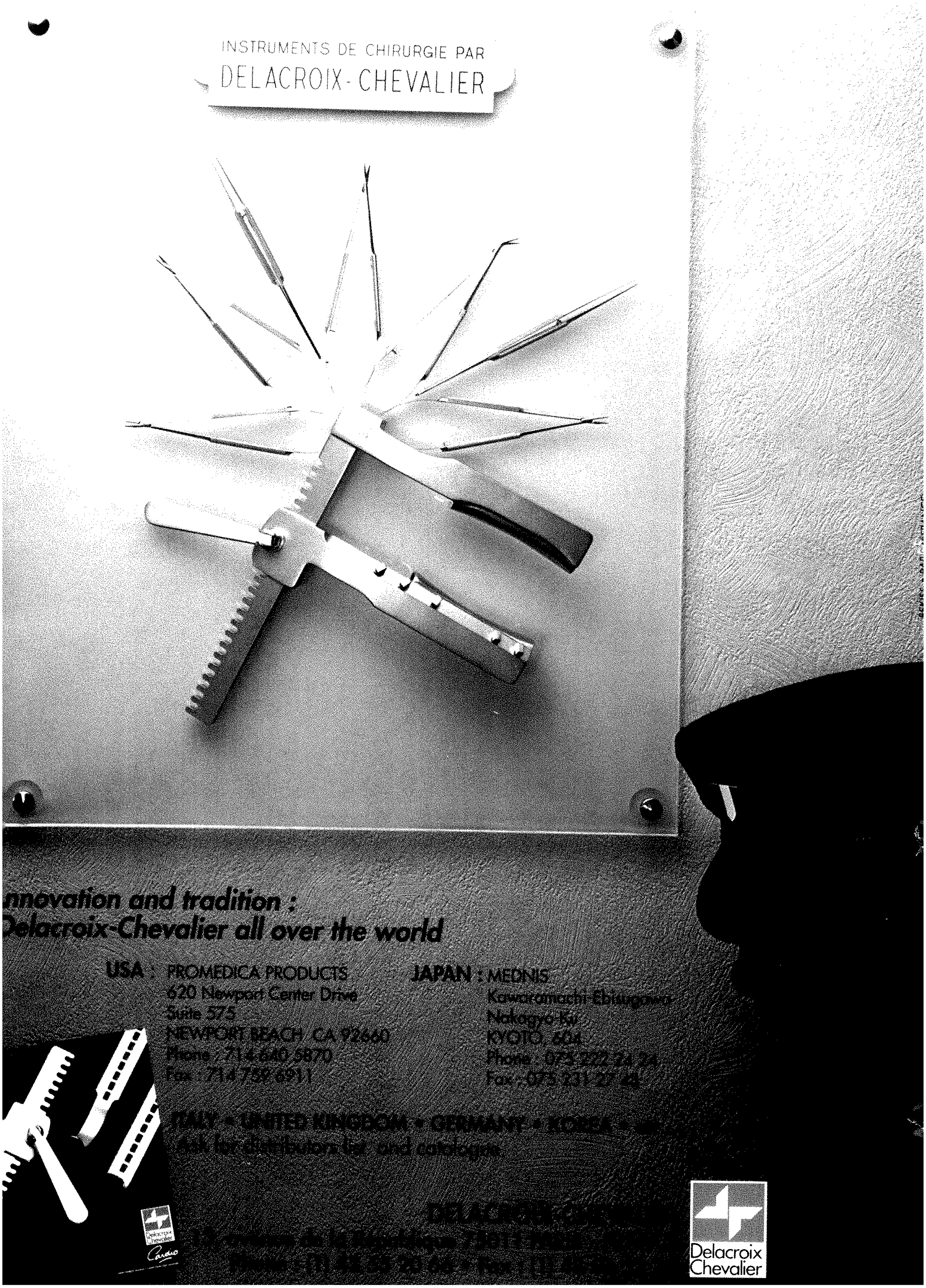

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Extracorporeal Membrane Oxygenation Revisited . . . Again

Carol Bosken, MD, and Claude Lenfant, MD

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Respiratory physicians have a distinguished record of achievement in the development and utilization of technology for mechanical ventilation. Indeed, the modern era of intensive care medicine would not be where it is today without the dedicated effort of many respiratory physiologists and physicians working to understand gas exchange in the very sick patient.

In the 1970s, the Division of Lung Diseases, National Heart, Lung, and Blood Institute (NHLBI), supported the development and testing of many types of respiratory equipment. In this era, evaluation of methods for ventilatory support was considered to be a major objective of the NHLBI national research program. Included in this effort was a multicenter controlled trial of extracorporeal membrane oxygenation (ECMO) for the treatment of the adult respiratory distress syndrome. Theoretically, ECMO offered many advantages over conventional respiratory support techniques, and there were preliminary reports of success from several institutions.

See also pages 553 and 738.

In early 1973, the NHLBI issued a request for contract proposals for a controlled, multicenter investigation to evaluate the possibility that ECMO could improve results of therapy in patients with adult respiratory distress syndrome. After a nationwide competition, nine clinical centers and a data center were selected to participate in this investigation. A study protocol was developed by a steering committee made up of the principal investigators. The protocol included strict criteria for patient selection, as well as ECMO equipment that met well-defined specifications. Before initiation of the study, the NHLBI appointed a Data Safety and Monitoring Board; this group approved the protocol for the ECMO study, and patient recruitment began in 1974.

A total of 90 patients were entered into the randomized study. Forty-two patients were randomized to ECMO therapy with mechanical ventilation and 48 to conventional (control) therapy. In the ECMO group, 4 patients survived; the same number survived in the control group. When reporting the results of the study, a preface stated [1]:

> The study was undertaken because a costly procedure was gaining ever wider use before there was clear evidence that it could achieve clinical results not attainable through more conventional therapeutic measures. The results of the ECMO trial should give pause to physicians who have regarded the ECMO as a suitable therapeutic intervention or who are entertaining the idea of using it for this purpose. It is abundantly clear that further research is needed and that ECMO must still be regarded as an experimental procedure.

We find ourselves today in an analogous position to that of 1973. Preliminary reports of a new form of extracorporeal life support with theoretical advantages over the older methods have shown promise in uncontrolled studies. The article in this issue of *The Annals of Thoracic Surgery* from the University of Michigan [2] describes successful treatment of 50% of patients with severe adult respiratory distress syndrome. This is similar to other uncontrolled studies showing up to 77% survival [3] and is truly remarkable if the patients and supportive therapy are equivalent to that used in the ECMO study, where the survival was less than 10%.

The uncontrolled studies frequently compare their results with the mortality figures from the 1974 to 1979 NHLBI ECMO study, and this procedure is justified on the basis that the current patients are selected using the "ECMO criteria." However, before accepting the validity of this comparison, we must examine the results of the selection process as well as the fidelity in applying the criteria. The ECMO criteria describe the severity of the pulmonary physiologic abnormality as defined by arterial blood gas results during conventional respirator therapy. Although these criteria are universally recognized as selecting patients with a poor prognosis, recent studies have refined our ability to predict mortality. It is now recognized that age [4], underlying disease [5], and the number of organs in addition to the lung that are dysfunctional [5] have significant impacts on outcome. Variation in the distribution of any of these variables could explain some of the differences in survival between study groups.

The original ECMO inclusion criteria are quite specific and comprehensive; however, the patients included in subsequent reports are not always as well described and sometimes do not fit the criteria precisely. For instance, the slow entry criteria in the ECMO trial required that the patients be treated with conventional therapy for at least 48 hours before institution of ECMO. In the final results, the mean duration of ventilator therapy before randomization was 7.23 days [1]. In the report in this issue of *The Annals*, 4 out of 5 of the survivors were ventilated for only 1 day before institution of extracorporeal life support. This high survival in patients who are treated early has been used as validation of the efficacy of therapy and as

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Ann Thorac Surg 1992;53:551–2

evidence that extracorporeal life support should be applied early before patients become moribund. However, the data do not exclude the possibility that the survivors were suffering from easily reversible acute abnormalities (such as fluid overload [7]), and that they would have responded to conventional therapy.

Changes in supportive therapy between the two study periods could also confound the analysis of relative mortality rates. Intensive care has undergone numerous improvements in the past 20 years, not the least of which is based on an understanding of the importance of infection as a complication of adult respiratory distress syndrome [8]. In addition to the use of newer antibiotics, supportive care has improved by maneuvers like discontinuing the use of H_2 blockers as prophylaxis against intestinal bleeding when they were shown to increase the rate of superinfection [9]. The effects of these changes can be seen in a recent summary of a large intensive care unit's experience treating adult respiratory distress syndrome. This unit has seen a fall in mortality from 65% in 1984 to 45% in 1991 (Hudson L; personal communication, 1991). Although this survey included patients who were less ill than those meeting ECMO criteria, it does demonstrate a change in the study population over the 7-year period.

Technical improvements have undoubtedly made extracorporeal life support safer, more effective, and easier to perform than ECMO. Nonetheless, the technique requires specialized equipment and highly skilled staff, and it still is associated with substantial mortality. In the 10 patients reported in this issue of *The Annals*, there were six serious/life-threatening complications. Even if bleeding can be reduced by the use of heparin-coated tubing [10], it will be important to carefully define the patients who will benefit from this type of therapy.

In the years since the initiation of the NHLBI ECMO trial, research into the underlying mechanisms that initiate and prolong respiratory failure has made giant advances. Mediators have been identified, and pharmacologic therapy directed against specific inflammatory pathways is currently being tested. Physicians are talking about prevention and early intervention rather than "rescue" and are designing strategies for clinical research projects with end points other than mortality. It is possible that the standard of care will change significantly in the next 10 years, making it difficult to predict what resources will be needed for prolonged respirator therapy in the future.

Extracorporeal oxygenation will remain among the armamentarium of respiratory and critical care physicians for some time, although the modern era will not include widespread use of this complex and invasive technology, especially if safe, inexpensive, and effective pharmacologic interventions become available. Experimental research on extracorporeal membrane oxygenators should also continue, as much information can be learned about functional and structural changes in critically ill patients. However, for this information to be useful it must be based on carefully designed protocols with detailed presentation of patient criteria instead of using the rubric of meeting "NHLBI ECMO criteria." Hopefully by combining investigation into basic mechanisms and improved supportive care, we will make significant headway against this devastating disease in the near future.

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Early Experience With Adult Extracorporeal Membrane Oxygenation in the Modern Era

Harry L. Anderson III, MD, Ralph E. Delius, MD, James M. Sinard, MD,
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In 1980 we stopped using extracorporeal membrane oxygenation for adults because only 1 of 20 patients treated between 1973 and 1979 survived. In October 1988 we returned to adult extracorporeal life support (ECLS) with a modified protocol including venovenous access when possible, large oxygenators for CO_2 clearance, activated clotting time of 180 to 200 seconds, and case selection based on 90% mortality (30% transpulmonary shunt). Of 19 patients referred, 14 met criteria for ECLS. Three of these 14 patients with isolated respiratory failure died before ECLS could be started, and 1 patient refused ECLS and died. Ten were placed on ECLS for 2 to 24 days. Indications were pneumonia (3), post-cardiac operation (2), and adult respiratory distress syndrome (5). Five recovered and 5 died. The cause of early death was progressive pulmonary injury (3), hemorrhage (1), and ventricular arrhythmia (1). One late death occurred at 3 months secondary to intraabdominal complications related to liver transplantation. In conclusion, 10 adult patients with severe respiratory failure were treated with extracorporeal life support; 5 patients recovered lung function and 4 of these patients survived and were discharged to home. Surviving patients were typically younger and were placed on ECLS early in their disease process, emphasizing that early intervention is one key factor to a successful outcome.

(Ann Thorac Surg 1992;53:553–63)

Prolonged extracorporeal circulation was first used successfully in the treatment of adult respiratory failure in 1971 [1]. Several other successful cases led to a National Institutes of Health (NIH)-sponsored multicenter, prospective, randomized trial in 1975 through 1978 [2]. The acronym ECMO for extracorporeal membrane oxygenation was adopted during this trial, although extracorporeal life support (ECLS) provides a more accurate description. Approximately 90% of the patients died in both the conventional treatment and ECMO groups. Although there were several problems with the design and implementation of the study, based on these results the technology was essentially abandoned in the United States in 1979. On the other hand, ECMO has become very successful in the management of neonatal respiratory failure [3]. Since the first case in 1975 [4], application of the technology has grown steadily. More than 5,900 patients have been treated in 80 active centers, with 80% to 90% survival of infants considered to be moribund with conventional ventilator management [5]. Two prospective, randomized studies in neonates [6, 7] confirm the benefit of ECMO over conventional treatment, and ECMO is now considered standard therapy.

See also pages 551 and 738.

Gattinoni, Kolobow, and their colleagues modified the ECMO procedure for adult patients, emphasizing CO_2 removal and venovenous access. In 1986 they reported 49% survival in 43 patients [8]. Their technique was evaluated in several other European centers with similar results. Using the selection criteria developed for the NIH ECMO study (90% mortality risk), several centers reported 50% survival [9].

Based on the results reported by Gattinoni and colleagues and the other European centers, and encouraged by the successful application of extracorporeal life support in our own neonatal [10] and pediatric population [11], in 1988 we developed a protocol for the evaluation of ECLS in adult respiratory failure. We planned to evaluate ECLS in 10 patients with severe respiratory failure, then review the experience. This is a report of that study.

Material and Methods

Selection Criteria

Criteria were very similar to those used for the NIH ECMO study and designed to detect patients with a high risk of mortality but with potentially reversible acute respiratory failure. Severity of disease was indicated by transpulmonary shunt greater than 30% or carbon dioxide tension greater than 44 mm Hg after and despite optimal ventilator and pharmacologic therapy. Thirty percent shunt corresponds to arterial oxygen saturation less than 0.95 at an inspired oxygen fraction of 1.0 and a venous

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oxygen saturation of 0.65. A third indicator of severe pulmonary dysfunction was effective compliance less than $0.5\ \mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{cm}\ H_2O^{-1}$. Potential for reversible disease was defined as age less than 60 years, days of mechanical ventilation less than 6, and no pharmacologic immunosuppression. Absolute contraindications were terminal disease or severe neurologic impairment, active bleeding prohibiting anticoagulation, and mechanical ventilation for more than 10 days. Optimal ventilator therapy was defined as the lowest inspired oxygen fraction sufficient to maintain arterial saturation greater than 0.95, optimal positive end-expiratory pressure and peak inspiratory pressure based on highest mixed venous oxygen saturation, and the tidal volume and rate adjusted to maintain carbon dioxide tension at 40 mm Hg or less without exceeding a peak inspiratory pressure of 50 cm H_2O. The definition of general optimal care included a total hemoglobin level of 120 to 150 g/L, localized infection treated by appropriate drainage, systemic infection treated with antibiotics, total enteral or parenteral nutrition, and sedation or paralysis to minimize metabolic rate.

Techniques of Extracorporeal Life Support

We planned to use the Gattinoni technique of venovenous access and low flow with CO_2 removal for all patients. Extracorporeal flow was increased until oxygen delivery was adequate to meet metabolic needs, resulting in high-flow venovenous ECLS for situations in which there was no transpulmonary gas exchange. Venoarterial access was used for patients with major cardiac and pulmonary failure, with planned conversion to venovenous access if and when cardiac function improved. Vascular access was achieved by direct exposure under local anesthesia using the right internal jugular vein as the venous drainage access of choice, and the right or left femoral vein was cannulated through the saphenous bulb for blood return. Arterial access, when necessary, was gained through the right common carotid artery or the common femoral artery. The distal jugular vein and carotid artery were ligated. The distal femoral artery was perfused from the circuit. A variety of catheters were used, selected on the basis of best pressure–flow characteristics. The circuit consisted of ⅜-inch polyvinyl chloride tubing, a roller pump servoregulated with a very small venous bladder, Tygon (Norton Performance Plastics, Akron, OH) in the pump raceway, SciMed (Avecor, Inc, Plymouth, MN) Kolobow membrane lungs, usually using two 4.5-m^2 membrane lungs in parallel, SciMed heat exchanger regulated to 37°C, and polyvinyl chloride arterial return tubing. In some cases Medtronic Maxima (Medtronic Blood Systems, Inc, Anaheim, CA) heparin-bonded capillary membrane lungs were used. The system was monitored by continuous preoxygenator and postoxygenator pressure monitors, and continuous mixed venous oxygen saturation was measured with an Oximetrix (Abbott Laboratories, North Chicago, IL) catheter placed in the venous drainage line. Extracorporeal flow was calculated from pump revolutions per minute and stroke volume. During priming the entire circuit was filled with carbon dioxide to minimize micro air bubbles. Carbon dioxide was then replaced with clear crystalloid prime. In most cases the clear prime was displaced with packed red blood cells and albumin solution with a final prime hematocrit of 0.20 to 0.30.

Once bypass was established, the extracorporeal flow was increased and ventilator settings decreased until low ventilator settings were achieved (inspired oxygen fraction <0.5, peak airway pressure <35 cm H_2O, rate <10/min). Extracorporeal flow was maintained with a primary goal of maintaining mixed venous oxygen saturation between 0.70 and 0.75 during venoarterial bypass and between 0.85 and 0.90 during venovenous bypass. A secondary goal for oxygenation was arterial saturation greater than 0.90. Membrane lung gas flow and composition were adjusted to maintain arterial carbon dioxide tension around 40 mm Hg. Heparin was administered continuously at a rate sufficient to maintain the whole blood activated clotting time between 180 and 200 seconds. Platelets were given as needed to maintain the platelet count at more than 70×10^9/L (70,000/μL). If bleeding occurred, it was managed by transfusing platelets to raise the platelet count to more than 100×10^9/L (100,000/μL), decreasing activated clotting time to 160 seconds, and surgical exploration of the bleeding site. If the patient was receiving inotropic drugs before ECLS, the infusion was gradually decreased and weaned off. Systemic perfusion was managed primarily by following mixed venous oxygen saturation and secondarily by monitoring acid-base status, mental function, and urinary output. Adequate systemic perfusion was maintained by cardiac function during venovenous bypass and by adjusting blood volume and flow during venoarterial bypass.

Most patients went through a period when there was essentially no pulmonary function. Improving lung function was detected by increased arterial oxygen tension or decreased carbon dioxide tension without any change in extracorporeal gas exchange or metabolic rate. As this occurred, extracorporeal flow was gradually decreased until most of the gas exchange took place through the native lung. When the level of extracorporeal support was 20% or less, the patient was tested off bypass, the so-called trial off. When the patient could maintain normal gas exchange at low ventilator settings without extracorporeal support, the catheters were removed. Femoral artery and vein were repaired if they had been used for vascular access. The jugular vein was repaired in selected patients.

Lung recovery was defined as normal gas exchange breathing room air without mechanical ventilation for 24 hours or more. Survival was defined as hospital discharge. All surviving patients have been followed up at regular intervals. Cause of death was determined in all patients who died. The design and protocol of this phase I evaluation were approved by the University of Michigan Institutional Review Board.

Results

We used ECLS for severe respiratory failure in 10 adult patients between October 1988 and September 1990. Four patients were referred from other institutions because of severe respiratory failure, and the remaining 6 patients were referred from within our institution. Three of these patients were referred from our own cardiac surgery service. During the same period, 9 additional patients were referred or considered for ECLS, but ECLS was not done because the patient died before or during transport or refused ECLS therapy, or because the patient had been on the ventilator more than 10 days. Of 6 patients for whom follow-up was available, all died of multiple organ failure.

The patients are described chronologically in Table 1. Early in our experience we used ECLS for patients who were outside of our predetermined criteria for potentially reversible lung disease. More recently we have held to the specific indications with better results. All patients had severe respiratory failure with an average shunt fraction of 42% ± 6% (mean ± standard error of the mean), alveolar-arterial oxygen pressure gradient of 588 ± 7 mm Hg, peak airway pressure of 63 ± 8 cm H_2O, and positive end-expiratory pressure of 14 ± 2 cm H_2O.

The course during extracorporeal life support in all patients is listed in Table 2. The average time on ECLS was 7.3 ± 2.2 days. Adequate gas exchange and perfusion support was achieved in all patients. Bleeding was considered serious enough to constitute a major complication in 3 patients. Major arrhythmias or cardiac arrest occurred in 3 patients. Although 2 patients were septic from the onset, there was only one episode of new onset of sepsis during ECLS. The most common mechanical complication was failure of the membrane lung, usually related to water accumulation in the gas phase. This complication was gradual in onset, easy to recognize, and managed successfully by changing the membrane lung in all instances. Another mechanical complication included pump failure, either by malfunction of the bladder box that controls the roller pump or loss of power at the roller pump.

Four patients died during ECLS: 2 patients with severe bacterial pneumonia died of progressive and overwhelming sepsis, both with no pulmonary function; 1 died of cardiac rupture during reexploration for pericardial bleeding; and 1 patient on venovenous bypass died of right heart failure and arrhythmia when total pulmonary fibrosis obliterated the pulmonary vasculature. One patient placed on ECLS for respiratory failure 7 days after a heart-lung transplant recovered pulmonary function, was weaned off venoarterial extracorporeal support, and had development of a fatal ventricular arrhythmia despite good pulmonary function shortly after decannulation. Lung recovery occurred in 5 patients, and 4 of these were ultimately discharged. The lung recovery patient who died was placed on ECLS for respiratory failure secondary to fulminant hepatic failure, which was in turn due to Wilson's disease. This patient received two liver transplants while on ECLS. Her pulmonary function recovered, but she died 3 months later of septic complications related to the liver transplant and associated immunosuppression. The first liver transplant did not function at all, and the second liver transplant never functioned normally. We consider three of the six deaths inevitable from total pulmonary failure and three of the six deaths caused in part by complications that may be preventable in the future.

Vascular access is listed in Table 3. Three patients had adequate cardiac function with respiratory failure only and were managed with venovenous bypass throughout the course of ECLS. One patient began with venovenous access but had development of cardiac failure requiring conversion to venoarterial bypass. Six patients had major cardiac instability when ECLS was instituted requiring venoarterial access. Two of these patients were converted to venovenous bypass when cardiac function improved.

Patients who recovered were generally younger, were on mechanical ventilation a shorter time, and had fewer contraindications to ECLS than patients who did not recover (Table 4). Each of the first 5 patients had at least one variable outside our set of predetermined reversible lung disease criteria. Only 1 of these patients recovered. For the next 5 patients we adhered more closely to the criteria of reversibility; only 1 of the 5 patients had a relative contraindication—systemic sepsis in the patient with pneumococcal pneumonia. The 4 patients without contraindications all survived.

The 4 long-term survivors all have normal neurologic function. All have normal pulmonary function on clinica examination, although all had radiographic evidence of pulmonary fibrosis at the time of hospital discharge. This radiographic abnormality has progressively returned toward normal in all patients. To date there has been one late complication: an infected pseudoaneurysm at the femoral artery access site, which was successfully repaired several months after the initial hospitalization.

Two representative cases are shown in Figures 1 through 4. Patient 1 (Figs 1, 2) was a 17-year-old girl with severe respiratory failure after multiple head, chest, abdominal, and orthopedic injuries from a motor vehicle accident. At the time of referral and institution of ECLS she had been on mechanical ventilation support with 100% oxygen and high pressure for 17 days. She was transferred to our institution after having undergone splenectomy for a ruptured spleen, and placement of bilateral chest tubes for pneumothoraces secondary to ventilator barotrauma during her postoperative period (see Fig 2A). Cardiac function was normal and she was cannulated for venovenous access through the right internal jugular vein for drainage and the right femoral vein for bypass reinfusion.

Her bypass course of 13 days was notable for persistence of bronchopleural fistulas bilaterally, lack of lung improvement as confirmed by the lack of transalveolar oxygenation, and bleeding from the cannulation sites and laparotomy site, which required reopening each of the wounds to achieve hemostasis (see Figs 2B, C). Other complications during her course included pump raceway rupture, loss of power at the roller pump requiring hand cranking of the pump, and two cardiac arrests near the conclusion of her bypass run. Because of the lack of pulmonary improvement and with increasing pulmonary artery pressures, bypass was electively terminated on day

Table 1. Characteristics of 10 Adult Patients Before Undergoing Extracorporeal Life Support for Cardiorespiratory Failure

							Ventilator Settings[a]					Last Blood Gas[a]					
Patient No.	Sex	Age (y)	Weight (kg)	Diagnoses	Origin	Contraindications	Vent Days	FiO_2	Rate (min^{-1})	PEEP (cm H_2O)	PIP (cm H_2O)	Sat	PO_2 (mm Hg)	PCO_2 (mm Hg)	pH	Q_s/Q_t	$P(A - a)O_2$
1	Female	17	56.8	Multiple trauma, pulm contusion	Outside	17 days ventilated	17	1	32	20	100	0.94	79	54	7.37	0.42	560
2	Female	37	85	CAD, postop CABG, pneumonia	UM	Necrotizing pneumonia	6	1	16	7	45	0.86	52	44	7.43	0.4	597
3	Female	32	78.1	Primary pulm HTN, heart-lung transplant	UM	Immunosuppression	8	1	40	15	60	0.92	66	51	7.38	0.31	576
4	Female	25	58.2	Wilson's disease, liver transplant × 2	UM	Immunosuppression	1	1	24	16	42	0.65	34	39	7.38	0.85	620
5	Male	67	84.1	CABG redo, arrest in OR, ARDS	UM	Age > 60 years	1	1	28	0	32	0.89	43	29	7.41	0.3	621
6	Male	29	85	Pancreatitis, ARDS	UM		1	1	40	22	84	0.94	77	21	7.38	0.3	595
7	Male	22	75	MVA, femur fracture, closed head injury	Outside		1	1	30	10	80	0.83	52	37	7.42	0.4	604
8	Male	35	75.9	MVA, left chest crush injury, pulm wedge resection	Outside		1	1	14	20	60	0.81	68	36	7.34	0.58	589
9	Male	23	60	Sickle cell, viral pneumonia, ARDS	Outside		4	1	16	15	85	0.90	60	44	7.37	0.3	589
				(second cannulation)			. . .	1	40	5	63	0.85	60	92	7.15	. . .	541
10	Female	53	58.9	Bacterial pneumonia	UM	Necrotizing pneumonia	5	1	40	15	47	0.93	75	44	7.32	0.34	574
Mean		34	71.7				4.5				63					0.42	588
Standard error		4.9	3.8				1.6				8					0.06	7

[a] Ventilator settings and blood gases are those just before initiation of extracorporeal life support.

ARDS = adult respiratory distress syndrome; CAD = coronary artery disease; CABG = coronary artery bypass grafting; FiO_2 = inspired oxygen fraction; HTN = hypertension; MVA = motor vehicle accident; OR = operating room; $P(A - a)O_2$ = alveolar-arterial oxygen gradient; PCO_2 = carbon dioxide tension; PEEP = posit? ive end-expiratory pressure; PIP = peak inspiratory pressure; PO_2 = oxygen tension; Sat = arterial oxygen saturation; Q_s/Q_t = pulmonary shunt fraction; UM = University of Michigan.

Table 2. Extracorporeal Life Support Courses of 10 Adult Patients With Cardiorespiratory Failure

Patient No.	Sex	Bypass Time (d)	VV/VA	Recovery/Survival	Special Procedures[a]	Complications[a]	Mode of Death
1	Female	13.1	VV	Died	None	BLD, pump failure, raceway rupture, cardiac arrest	Elective termination
2	Female	0.8	VV	Died	None	Cardiac arrest	Elective termination
3	Female	7.8	VA	Died	None	Femoral artery dissection, BLD, cardiac arrest	Vent dysrhythmia after decannulation
4	Female	3.8	VA	Lung recovery (LD)	OR—liver transplant × 2 on ECLS	Renal failure	Late death
5	Male	2.8	VA	Died	OR—mediastinal exploration on ECLS	BLD (hemothorax), died in OR (bleeding)	Died in OR
6	Male	3.1	VA	Survived	Medtronics heparin-bonded lung	Renal failure, oxygenator failure, oxygenator plasma leak	
7	Male	2	VV	Survived	Transport on ECLS		
8	Male	5.8	VA → VV	Survived	Transport on ECLS, percutaneous trach	Trach airway plug	
9	Male	22.2	VV → VA → VV		Transport on ECLS, open lung biopsy	Circuit change × 3, air embolus	
		1.8	VA	Survived	Recannulated—respiratory failure		
10	Female	10	VA → VV	Died	Medtronics heparin-bonded lung	Oxygenator failure × 2	Elective termination
Mean		7.3					
Standard error		2.2					

[a] Special procedures and complications are those that occurred during the bypass course.

BLD = bleeding; ECLS = extracorporeal life support; LD = late death; OR = operating room; trach = tracheostomy; VA = venoarterial bypass; vent = ventricular; VV = venovenous bypass.

Table 3. Vascular Access for 10 Adult Patients on Extracorporeal Life Support[a]

Bypass Mode	n	Recovered	Survived
VA	4	2	1
VV	3	1	1
VA → VV	2	1	1
VV → VA	1	1	1
Total	10	5	4

[a] Cannulation was performed using the internal jugular vein or femoral veins for venoarterial (VA) or venovenous (VV) drainage. Venovenous reinfusion was accomplished using cannulation of femoral veins. Venoarterial reinfusion was accomplished using cannulation of the right common carotid or common femoral arteries. Recovery is defined as wean to room air for at least 24 hours. Survival is defined as discharge to home.

13 and she died. Autopsy revealed substantial pulmonary fibrosis and congestion with a small intracerebral bleed.

Patient 9 (Figs 3, 4) is a 23-year-old man with an underlying history of sickle cell disease in whom sudden severe respiratory failure developed, presumably caused by viral pneumonia (which was never proven by viral cultures or titers; see Fig 4A). Because of the severity of respiratory failure immediate transportation using mechanical ventilation was considered impossible, and he was begun on ECLS with venoarterial access at the initiating hospital, then transferred by ground ambulance to our hospital on extracorporeal support. On day 3 he underwent open lung biopsy while on bypass which showed no fibrosis and no evidence of sickle cell pulmonary disease. His cardiac function improved and he was converted to venovenous access on day 6. On day 8 a groin access site was explored for bleeding, and on day 9 a tracheostomy was placed by percutaneous technique. On days 21 and 22 pulmonary improvement was demonstrated during trials off from bypass, thus decannulation was performed (see Fig 4C). Because of an apparent air embolus introduced during removal of the right internal jugular catheter, respiratory failure reappeared and the patient was placed on venoarterial bypass using femoral artery and vein access. After 43 hours of ECLS support, he was decannulated, and eventually weaned from the ventilator 3 weeks later. One month after discontinuation of ECLS support he was discharged from the hospital and continues to do well.

Table 4. Results of 10 Adult Patients Undergoing Extracorporeal Life Support for Cardiorespiratory Failure[a]

Variable	Recovered	Survived	Died
No. of patients	5	4	6
Age (y)	26.8 ± 2.4	27.3 ± 3.0	38.5 ± 7.6
Days mechanical ventilation before ECLS	1.6	1.8	6.3
ECLS bypass time (d)	7.7 ± 4.1	8.7 ± 5.2	6.4 ± 1.9
Patients with contraindications to ECLS	1	0	6

[a] Listed are the number of patients with contraindications to ECLS (greater than 5 days mechanical ventilation, greater than 60 years of age, poor prognosis for quality of life, immune suppression, or necrotizing pneumonia; see text) and the outcome of the ECLS course. Recovery is defined as wean to room air for at least 24 hours. Survival is defined as discharge to home. (Mean values are expressed as the mean ± standard error of the mean.)

ECLS = extracorporeal life support.

Comment

A nationwide epidemic of viral pneumonia occurred in 1976, and these patients dominated the NIH-sponsored adult ECMO study. Some of the nine study centers were inexperienced, coagulation control was crude, venoarterial bypass was used, and many of the patients were maintained on high-pressure, high-oxygen mechanical ventilation [12]. Looking back on this experience, it is somewhat surprising that any patients survived. Gattinoni and Kolobow hypothesized that many of the problems in the initial study could be addressed by the use of low-flow extracorporeal circulation with venovenous access permitting full pulmonary blood flow while eliminating all the metabolically produced CO_2. This in turn eliminated the need for mechanical ventilation and allowed emphasis on continuous pressure inflation without peak inspiratory pressures to cause alveolar overdistention. The first report on this new technique was very encouraging [8], and other reports soon followed [9]. Morris pointed out that these improved results may be related to improved methods of mechanical ventilation and other aspects of patient management, as well as extracorporeal support. He designed and began another prospective randomized study including a tightly structured algorithm for management and mechanical ventilation [13]. That randomized study is currently underway in Salt Lake City. The Gattinoni method and the Morris protocol are limited to venovenous access only.

We returned to the evaluation of ECLS in adult respiratory failure after a hiatus of 8 years because there were reasons to believe that we could improve on the original 10% survival rate. The rationale of the Gattinoni approach was sound, and the results from several centers supported this rationale. The widespread success of extracorporeal support in neonatal respiratory failure indicated that complications were minimal, coagulation control was significantly improved, and the technique could be managed safely with a low incidence of mechanical complications. Finally, we had in place a large team of extracorporeal specialists with experience in more than 200 neonatal and pediatric cases. Our criteria selected patients with very high mortality risk. Although the threshold limit was set at 30% transpulmonary shunt, the actual shunt fraction of the ECLS patients at the time bypass was instituted was 42%. Five of the patients were in extremis with venoarterial ECLS instituted in emergent circumstances as part of the resuscitation. All of the patients progressed to a condition of minimal or no pulmonary gas exchange for the first few days on extracorporeal support. Nine other

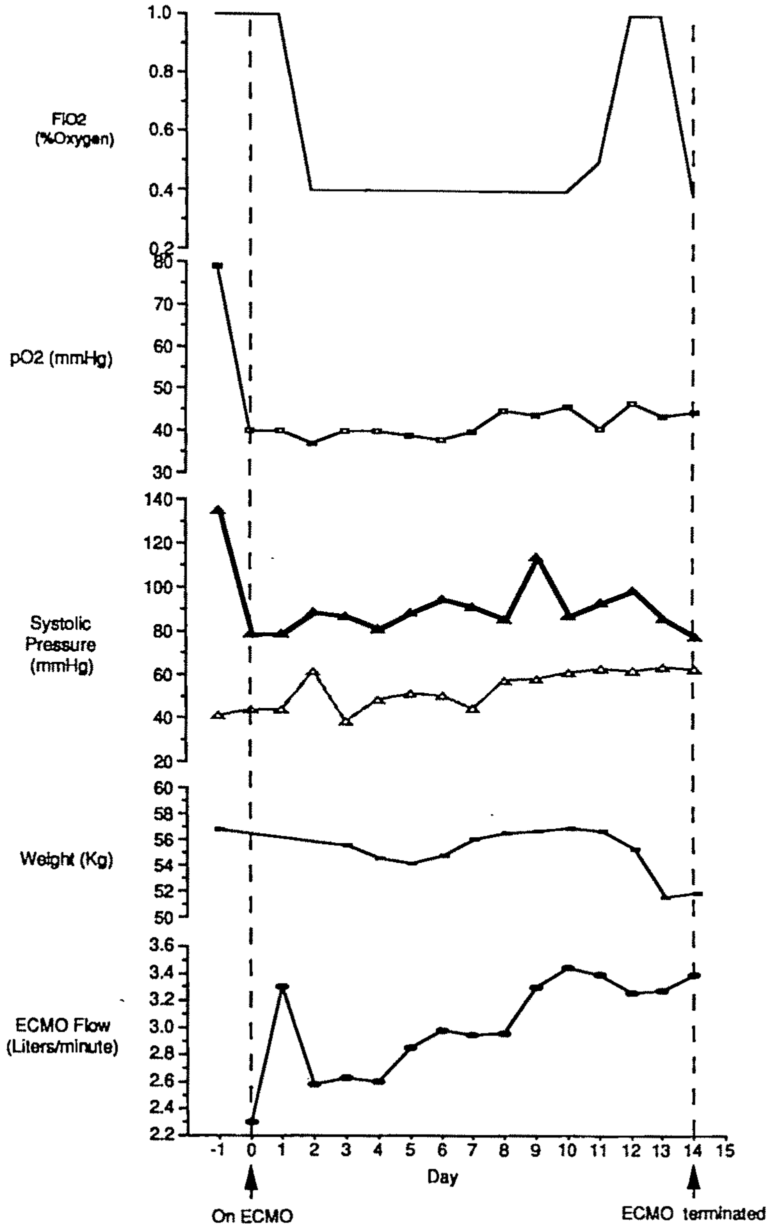


Fig 1. Graphical representation of patient 1 undergoing venovenous extracorporeal membrane oxygenatior (ECMO) for ventilator-induced barotrauma and respiratory failure 17 days after a motor vehicle accident. Inspired oxygen concentration, (FiO2), arterial oxygen tension (pO2), systolic arterial (▲) and pulmonary arterial (△) pressures, weight, and ECMO pump flow are plotted against time. Support was stopped after 13 days of venovenous support with no improvement in lung function and after two cardiac arrests while on bypass.

patients were referred or considered for ECLS based on the same physiologic criteria; at least 6 of these died. This study was designed as a phase I evaluation of safety and efficacy of ECLS using newer techniques. There was no randomization and no control group. These 10 patients represent a diverse number of diagnoses, and patients undergoing either venoarterial or venovenous bypass are presented as a single group. These patients were homogeneous to the extent that they were all initially at high risk of dying due to severe respiratory failure.

Why is the recovery and survival rate with ECLS improved from 10% ten years ago to 50% now? First, the selection criteria may not indicate 90% mortality risk. Perhaps the 5 patients who recovered would have recovered without ECLS. The uniformly high mortality in the patients who met criteria but were not treated with ECLS indicates that these criteria do indeed select patients wit a very high mortality risk. Second, perhaps a trial c pressure-support, inverse ratio, or some other mode c mechanical ventilation might have been equally successful. This possibility is being tested in the Morris study Third, the management of ECLS is much better now tha it was 10 years ago. The average blood transfusion requirement in the NIH ECMO study was 2 L/day; in ou study it was less than 300 mL/day. Airway pressure an inspired oxygen fraction are routinely reduced to nor damaging levels, unlike the earlier study. Mechanica complications are less serious and easily managed. large, experienced team helps to minimize human error secondary to fatigue or inexperience. Fourth, venovenou access maintains normal pulmonary blood flow in th peripheral lung capillaries, which might thrombose unde

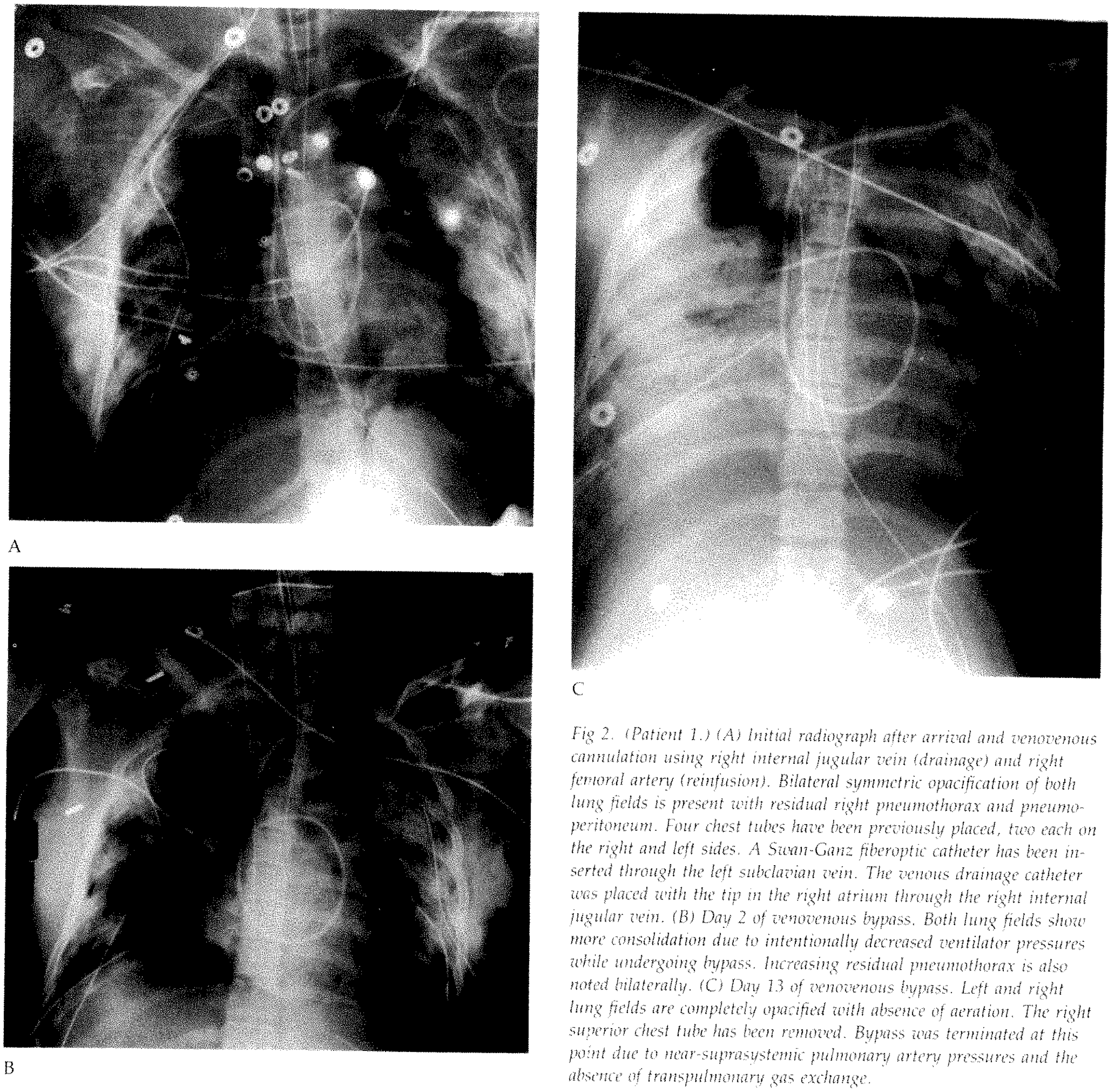


Fig 2. (Patient 1.) (A) Initial radiograph after arrival and venovenous cannulation using right internal jugular vein (drainage) and right femoral artery (reinfusion). Bilateral symmetric opacification of both lung fields is present with residual right pneumothorax and pneumoperitoneum. Four chest tubes have been previously placed, two each on the right and left sides. A Swan-Ganz fiberoptic catheter has been inserted through the left subclavian vein. The venous drainage catheter was placed with the tip in the right atrium through the right internal jugular vein. (B) Day 2 of venovenous bypass. Both lung fields show more consolidation due to intentionally decreased ventilator pressures while undergoing bypass. Increasing residual pneumothorax is also noted bilaterally. (C) Day 13 of venovenous bypass. Left and right lung fields are completely opacified with absence of aeration. The right superior chest tube has been removed. Bypass was terminated at this point due to near-suprasystemic pulmonary artery pressures and the absence of transpulmonary gas exchange.

conditions of low blood flow during venoarterial access. Moreover, the platelet/white cell microemboli and other bits of embolic material that inevitably form during extracorporeal circulation are filtered through the pulmonary capillary bed during venovenous bypass; they are perfused directly into the systemic capillary bed during venoarterial bypass. This phenomenon may have led to systemic organ malfunction during prolonged venoarterial bypass in the NIH ECMO study. Fifth, in our own series reported here, the use of venoarterial bypass for cardiac support and resuscitation and the use of ECLS during patient transport seemed to be important factors in the recovery of our patients. Our experience in neonates (in whom venovenous is now used routinely as the primary choice for access) and in older children (in whom both venovenous and venoarterial access are used) indicates that the full armamentarium of extracorporeal support is necessary to manage the full spectrum of patients and disease. Common carotid artery cannulation was used during venoarterial bypass in 4 patients. The common carotid artery can accomodate a relatively large reinfusion catheter and is easily used as there is abundant collateral flow about this vessel distally to the brain when it is ligated at cannulation. When possible during routine cannulation, the awake patient is asked to move the contralateral side after temporary clamping of the common carotid artery to assure sufficient collateral circulation before ligation of the vessel. At decannulation the common carotid artery is not repaired. It is ligated proximally. Although the long-term consequences of common

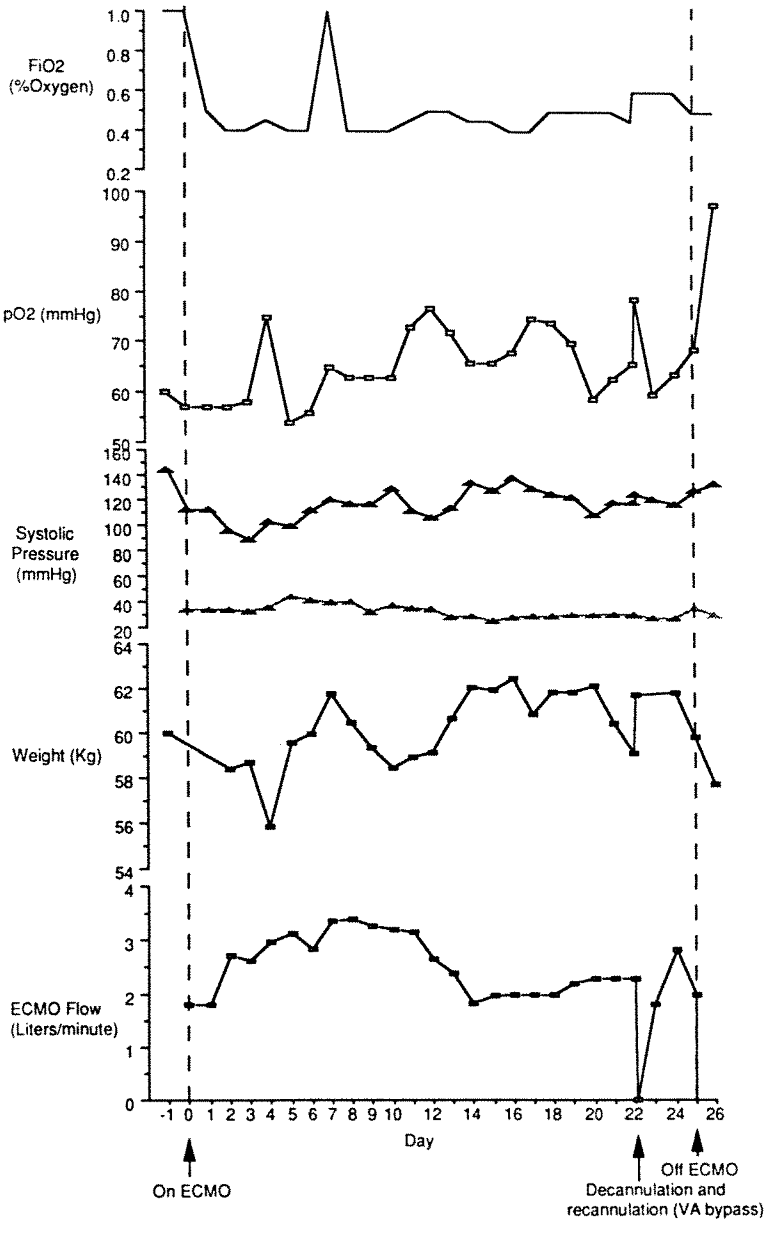
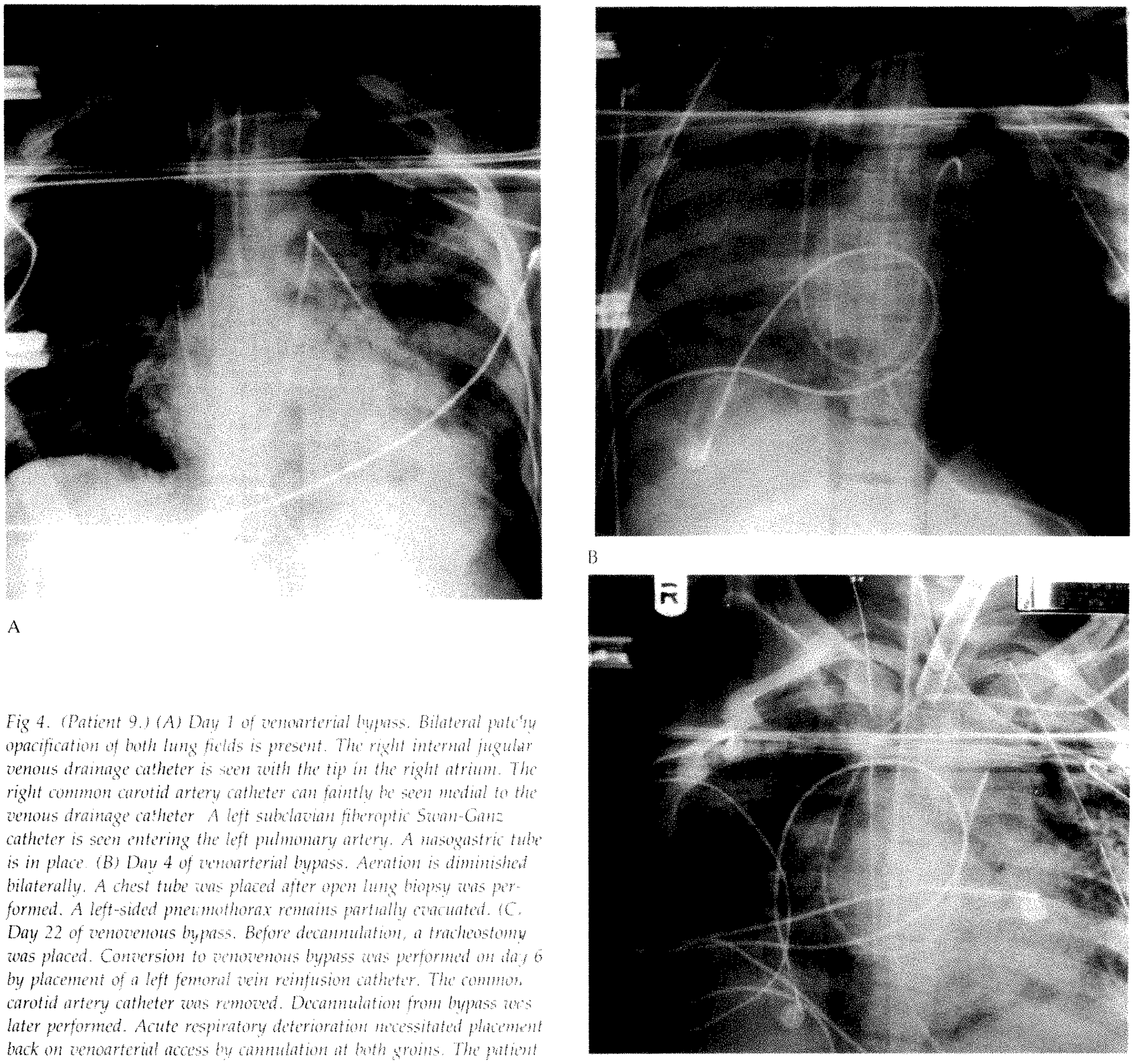


*Fig 3. Graphical representation of patient 9 with sickle cell disease undergoing extracorporeal membrane oxygenation (*ECMO*) for respiratory failure due to an apparent viral pneumonia. The patient was cannulated for venoarterial bypass for transport from an outside hospital and later switched to venovenous bypass on day 6. Decannulation was performed on day 22; however, the patient was placed back on venoarterial bypass when an air embolus was introduced during removal of the right internal jugular catheter. The patient was later converted to venovenous bypass and was decannulated 2 days later. Inspired oxygen concentration (*FiO2*), arterial oxygen tension (*pO2*), systolic arterial (*▲*) and pulmonary arterial (*△*) pressures, weight, and ECMO pump flow are plotted against time.*

carotid artery ligation in the adult are not known, it appears to be relatively well tolerated in the newborn and pediatric patient, in whom carotid artery cannulation is routinely selected for use during venoarterial bypass. Newborn or pediatric patients previously undergoing carotid artery cannulation have only been followed up to their current age of about 15 years, and there appear to be no long-term sequelae.

Administration of a program in extracorporeal life support is not without cost. Our program comprises full-time physicians (medical and surgical) and nurses, respiratory therapists, and perfusionists, who fill roles in both program administration and bedside operation of the pump. Currently we have 15 full-time and 32 part-time "ECLS specialists" with the capability of concurrently treating a maximum of 5 patients. Added daily costs of ECLS to the patient amount to approximately $4,500.00 for the initiation of bypass and approximately $2,500.00 a day while being maintained on ECLS bypass. In the neonate, this cost of ECLS is balanced by decreased intensive care unit and hospital stay. Full-time commitment of trained personnel and designated equipment for ECLS bypass is a requirement for success of this type of critical care support technology.

Based on this experience and on reports from other centers, it appears that extracorporeal life support will have a role in the management of acute respiratory failure in adults. At least, clinical evaluation of the procedure should be encouraged at major medical centers where the technology can be properly developed and studied. At most, it should be included in the management algorithm of patients who are known to be at 80% or greater



A

B

C

Fig 4. (Patient 9.) (A) Day 1 of venoarterial bypass. Bilateral patchy opacification of both lung fields is present. The right internal jugular venous drainage catheter is seen with the tip in the right atrium. The right common carotid artery catheter can faintly be seen medial to the venous drainage catheter. A left subclavian fiberoptic Swan-Ganz catheter is seen entering the left pulmonary artery. A nasogastric tube is in place. (B) Day 4 of venoarterial bypass. Aeration is diminished bilaterally. A chest tube was placed after open lung biopsy was performed. A left-sided pneumothorax remains partially evacuated. (C) Day 22 of venovenous bypass. Before decannulation, a tracheostomy was placed. Conversion to venovenous bypass was performed on day 6 by placement of a left femoral vein reinfusion catheter. The common carotid artery catheter was removed. Decannulation from bypass was later performed. Acute respiratory deterioration necessitated placement back on venoarterial access by cannulation at both groins. The patient ultimately was again decannulated and was discharged to home.

mortality risk, but still at a stage when lung injury is reversible. Specific identification of both mortality risk and reversibility remains a major challenge to clinical investigators. The Morris study will define the mortality risk for patients who meet the 1975 NIH ECMO criteria, provided these patients are treated according to the carefully defined algorithm in Salt Lake City. Other major centers should define the mortality risk of specific physiologic milestones in their own hospitals with the intent of determining the incidence, severity, and mortality of acute respiratory failure under specific treatment regimens. This information will be essential for planning clinical studies of ECLS as the technology develops. The Morris study will determine the effectiveness of low-flow venovenous ECLS for CO_2 removal in their population of patients. However the technology is changing rapidly and that specific question may be of minor importance by the time that study is completed. Our experience indicates that the full spectrum of ECLS techniques is required for successful management. More importantly, the impact of heparin-bonded circuits, new membrane lungs, on-line venous oxygen saturation monitoring, and patient transport on ECLS remains to be determined. More prospective, controlled, randomized studies should be done, but heeding the lessons learned from the last 10 years of prospective, randomized trials of ECMO [2, 6, 7, 14]. New studies should be done when the technology is stable and standardized, when experienced, well-supported clinical teams are established, when "conventional" therapy can be standardized and the results of conventional therapy characterized, and when phase I clinical ECLS studies indicate which high mortality risk patients are likely to have reversible lung injury. While existing treatment and ECLS techniques are becoming standardized and while these data are being collected, phase I studies of safety and efficacy should continue. Specifically, it is reasonable to use ECLS as rescue treatment for moribund patients with reversible disease (as best as that can be determined).

In conclusion, 10 adult patients were treated with ECLS for severe respiratory failure; 5 recovered and 4 survived. Recovery and survival was associated with short duration of mechanical ventilation, young age, and no immunosuppression. The improved results with ECLS, both in our series and in reports from other centers, appear to be due to improved technology, improved patient selection, and better understanding of physiology, pathophysiology, and the management during ECLS. As ECLS technology and indications evolve, a trial of ECLS is a reasonable alternative to continuing conventional treatment in moribund patients. When the technology is stable and when mortality indicators with conventional treatment are defined, prospective, randomized studies should be undertaken.

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DISCUSSION

DR ALEXANDER S. GEHA (Cleveland, OH): Thank you, Dr Anderson, for this important report, bringing back ECMO in a bit more defined way for adult support. At this time can you say something or prognosticate as to the type of patient in whom this technology is going to be most indicated, and the patient in whom it would be contraindicated?

DR ANDERSON: I guess there is no *one* type of patient who will benefit most from ECMO. The ones who will most likely recover lung function and survive are those who, as we have said, hav been intubated and mechanically ventilated a short period time. Usually this includes patients with pure capillary lea syndrome or adult respiratory distress syndrome, but even thi can cover a wider spectrum of disease—postoperative, postope ative cardiac, or even conventional pneumonia. But I think th take home message is that they have to be put on ECMO early i the disease process as opposed to late.

Surgical Therapy of Paroxysmal Atrial Fibrillation With the "Corridor" Operation

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Patients with paroxysmal atrial fibrillation may be extremely disabled despite medical therapy. Based on recent concepts of atrial fibrillation, a surgical open heart procedure was designed to isolate a "corridor" from the right and the left atrium. The corridor consists of the sinus node area, the atrioventricular nodal junction, and the connecting right atrial mass, small enough to prevent atrial fibrillation. Between 1987 and 1990, 20 patients with severely disabling symptoms due to frequent paroxysmal atrial fibrillation underwent the corridor operation, with permanent success in 16 patients. In 8 patients, left atrium to corridor conduction reappeared shortly after the procedure. Reoperation was performed in these patients without extracorporeal circulation. The site of persistent conduction between the left atrium and the corridor could consistently be localized adjacent to the coronary sinus. Nevertheless, reoperation failed to isolate permanently the corridor in 4 patients. During a mean follow-up of 20 months, atrial fibrillation dominating the ventricles was never observed nor inducible in the corridor in the 16 patients with a successful operation. In all cured patients, sinus node function remained undisturbed. Paroxysmal atrial flutter inside the corridor arose in 1 patient and a paroxysmal focal tachycardia in another. All 16 cured patients experienced a clear improvement in quality of life. Refinement of the surgical technique to obtain persistent isolation between the left atrium and the corridor is needed. These results demonstrate that the concept of the corridor operation is sound and justify its use in the treatment of drug-refractory paroxysmal atrial fibrillation.

(Ann Thorac Surg 1992;53:564–71)

Despite thorough antiarrhythmic drug trials, paroxysmal atrial fibrillation (AF) can often and seriously interrupt daily duties and life-style. Loss of normal atrial activation diminishing cardiac output by as much as 20% is considered one of the important causes of these symptoms [1, 2]. His bundle ablation by catheter shock [3] or by operation [4] is today the final therapeutical option, but it sacrifices the benefits of sinus node function. His bundle ablation indeed allows control of the heart rate only at the price of pacemaker dependency.

The perpetuation of AF has been proved to depend on a critical number of wavelets in the atria that continuously change in dimension and orientation [5, 6]. This concept of "the leading circle" implies that reduction of atrial surface area may inhibit the initiation and perpetuation of AF because a smaller area cannot harbor a sufficient number of wavelets [6].

We have designed a surgical technique—the corridor operation [7, 8]—that preserves the function of the sinus node and propagation of its impulses to the ventricles by insulating a segment of atria harboring the sinus node, the atrioventricular (AV) nodal region, and a bridge of atrial tissue between the two, while protecting the corridor function from interference of possible coexistent fibrillation in the rest of the atria. This study reports on our further experience [9, 10] with the corridor procedure in the first 20 consecutive patients with drug-refractory paroxysmal AF.

Material and Methods

Patient Population

Between April 1987 and December 1989, 20 patients (14 male, 6 female) varying in age from 32 to 69 years (Table 1) were operated on at the St Antonius Hospital. All patients had paroxysmal AF for at least 3 years, causing dizziness, loss of exercise tolerance, and extreme fatigue. Between episodes of the arrhythmia, all patients had a normal life-style. At least four antiarrhythmic drugs, including amiodarone, failed to suppress AF.

Three patients had associated cardiac disease: an open foramen ovale, mild mitral, and mild aortic valve regurgitation, respectively. Preoperative echocardiographic, hemodynamic, and angiographic studies showed normal anatomy and function of the heart in 17 patients. Four patients had previous attempted His bundle catheter ablation. All patients gave informed consent recognizing the experimental nature of the corridor operation.

Preoperative Rhythm Studies

Paroxysmal AF was documented by standard electrocardiographic recordings, Holter recordings, and bicycle

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Table 1. In-Hospital Results of the Corridor Procedure

Patient No.	Age (y)	Site of Postoperative Connection	Inducible Arrhythmia in Corridor	Spontaneous New Arrhythmia Before Discharge	Basic Rhythm at Discharge	Antiarrhythmi Drug or Pacemaker at Discharge
1	69	. . .	. . .	. . .	SR	. . .
2	51	LA-corr at CS	. . .	. . .	SR	. . .
3	59	. . .	. . .	. . .	SR	. . .
4	48	. . .	. . .	. . .	SR	. . .
5	58	. . .	. . .	. . .	AV nodal	. . .
6	51	. . .	. . .	. . .	SR	. . .
7	57	LA-corr at CS	. . .	. . .	SR	. . .
8	68	. . .	. . .	. . .	SR	. . .
9	68	LA-corr at CS	. . .	. . .	SR	. . .
10	45	. . .	Flutter in corridor	. . .	SR	. . .
11	32	LA-corr at CS	. . .	. . .	SR	. . .
12	45	LA-corr at CS	. . .	. . .	Flutter in LA	Flecainide
13	45	. . .	. . .	. . .	AV nodal	. . .
14	43	. . .	. . .	. . .	SR	. . .
15	45	. . .	. . .	Focal tachycardia in corridor	SR	Quinidine
16	57	. . .	. . .	. . .	SR	. . .
17	59	LA-corr site?	. . .	. . .	AV nodal	VVIR
18	49	LA-corr at CS	. . .	Paroxysmal AF	SR	Disopyramide
19	52	. . .	. . .	. . .	SR	. . .
20	36	LA-corr at CS	. . .	. . .	AV nodal	VVIR

AF = atrial fibrillation; AV = atrioventricular; CS = coronary sinus; LA-corr = left-atrium to corridor; SR = sinus rhythm; VVIR rate-modulated ventricular pacemaker.

stress testing. Heart rate varying at rest between 60 and 120 beats/min, without medication, was considered normal sinus activity as well as a corrected sinus node recovery time less than 550 milliseconds, determined by the conventional method [11]. Normal AV conduction was defined as 1:1 conduction to at least 140 beats/min during sinus rhythm or atrial stimulation. Presence of accessory AV nodal pathways was excluded with programmed electrical stimulation (PES) using standard methods [11]. All observations were carried out after withdrawal of antiarrhythmic drugs, eg, amiodarone administration was stopped at least 3 months before operation.

Surgical Procedure

After median sternotomy, institution of cardiopulmonary bypass, and cold cardioplegic cardiac arrest, the corridor procedure is carried out in two steps. The right atrium is incised next to the atrial appendage down to the interatrial groove. This incision is extended to the anterior and to the posterior side of the AV junction. The incision lies just lateral to the fossa ovalis and reaches the posterior AV junction just lateral to the orifice of the coronary sinus. On the anterior side the incision reaches the tricuspid ring as medial as possible, preserving the sinus node artery (Fig 1). In a second step the left atrial incision is started in the interatrial groove and carried out further to the roof of the left atrium under the superior caval vein. It is prolonge behind the aorta, cutting the atrial wall from the insid until it reaches the mitral valve ring. It lies in fron anterior to the left atrial appendage. On the posterior sic the incision is extended downward to reach the mitr valve ring next to the interatrial septum, near th posteromedial commissure (Fig 2). The coronary sinus identified (Fig 3). Uttermost care was taken to spare th sinus node artery. Before resuturing the atrial incisions restore the atrial anatomy, cryocoagulation is additional carried out at the four sites where the incisions reach th AV sulcus to ensure complete electrical isolation.

Intraoperative Electrophysiologic Study

After normothermic reperfusion of the heart, the electric isolation of the left atrium, the corridor, and the residu right atrium is tested by successive pacing of each of th three compartments. Absence of propagation of induce beats from one to another compartment and propagatic of impulses to the ventricles by stimulation of the corrid permits us to verify completeness of isolation. Increme tal pacing of the corridor enables us to establish th properties of AV conduction. When complete isolation obtained, the extracorporeal circulation is discontinue Temporary epicardial wires are attached to the left atriur the corridor, the residual right atrium, and the rig ventricle for postoperative PES.

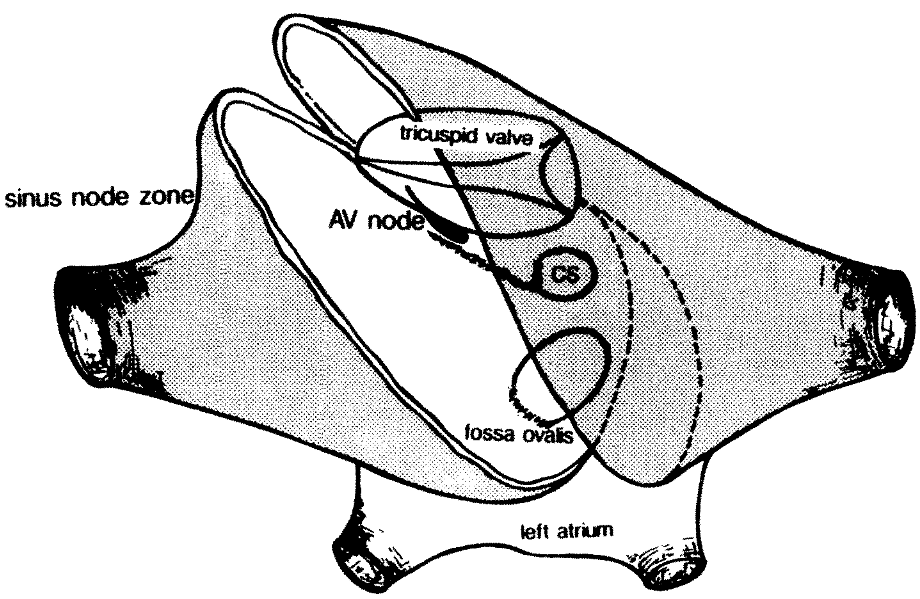

Fig 1. Schematic display of the right atrial incision. The right atrium is incised next to the atrial appendage down to the interatrial groove. The fossa ovalis is kept at the medial side of the incision as well as the orifice of the coronary sinus (CS). The incision is extended to reach the tricuspid ring at the atrioventricular junction, at which site an additional cryoablation is performed. The atrial part that becomes the corridor comprises the sinus node zone, the atrioventricular nodal (AV node) *region, and the orifice of the coronary sinus.*

Postoperative In-Hospital Studies

Apart from continuous rhythm monitoring, PES using the epicardial wires was routinely carried out at days 1, 3, 5, and 7 after operation. Multichannel recordings including five standard electrocardiographic leads and the bipolar epicardial signals from the left atrium, the corridor, the residual right atrium, and the right ventricle were written on a chart recorder (paper speed, 100 mm/s). This was done to check the completeness of the isolation and to establish the behavior of the sinus node and AV conduction. Programmed electrical stimulation of the various compartments was carried out to check the isolation at rapid rhythms. Induction of AF or other atrial arrhythmias such as atrial flutter was attempted in each atrial compartment. Before discharge, temporary wires were removed. In addition to standard postoperative care, all patients received anticoagulant therapy using warfarin for 3 months postoperatively.

Long-Term Follow-up

All patients have been reviewed every 3 months after discharge. Arrhythmias, exercise tolerance, and quality of life were assessed. Arrhythmias and the function of sinus node and AV node were assessed by standard electrocardiography, Holter recordings, and bicycle stress testing.

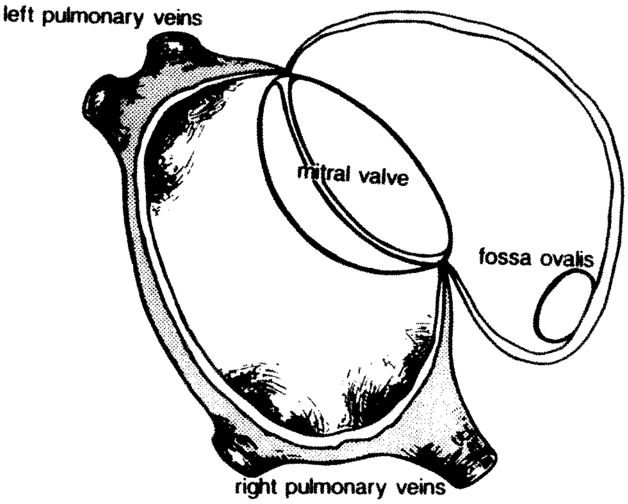

Fig 2. Schematic display of the left atrial incision. The left atrium is incised anterior to the right pulmonary veins in the interatrial groove. The incision is extended upward, under the superior caval vein to the roof of the left atrium, and extended to reach the mitral valve ring, anterior to the orifice of the left atrial appendage. The incision is extended posteriorly to reach the mitral valve ring next to the interatrial septum. An additional cryoablation is performed at the site where the incision reaches the mitral ring.

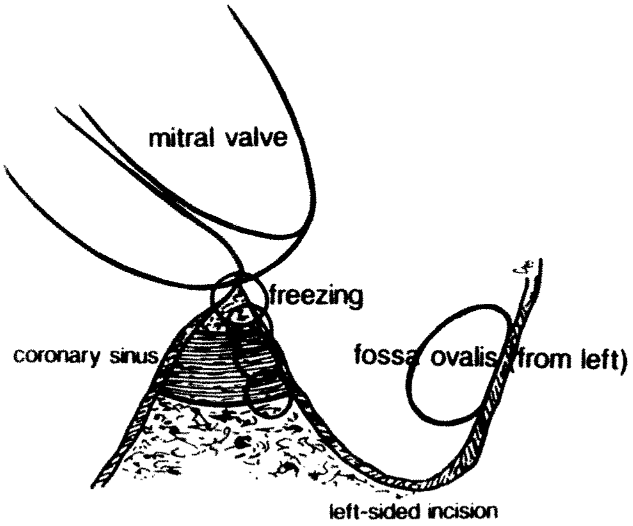

Fig 3. Detail of the posterior side of the left atrial incision. The incision of the atrial wall is carried out from the inside and the coronary sinus is visualized. Care is taken not to sever this structure. An additional freezing of the coronary sinus at this point is performed.

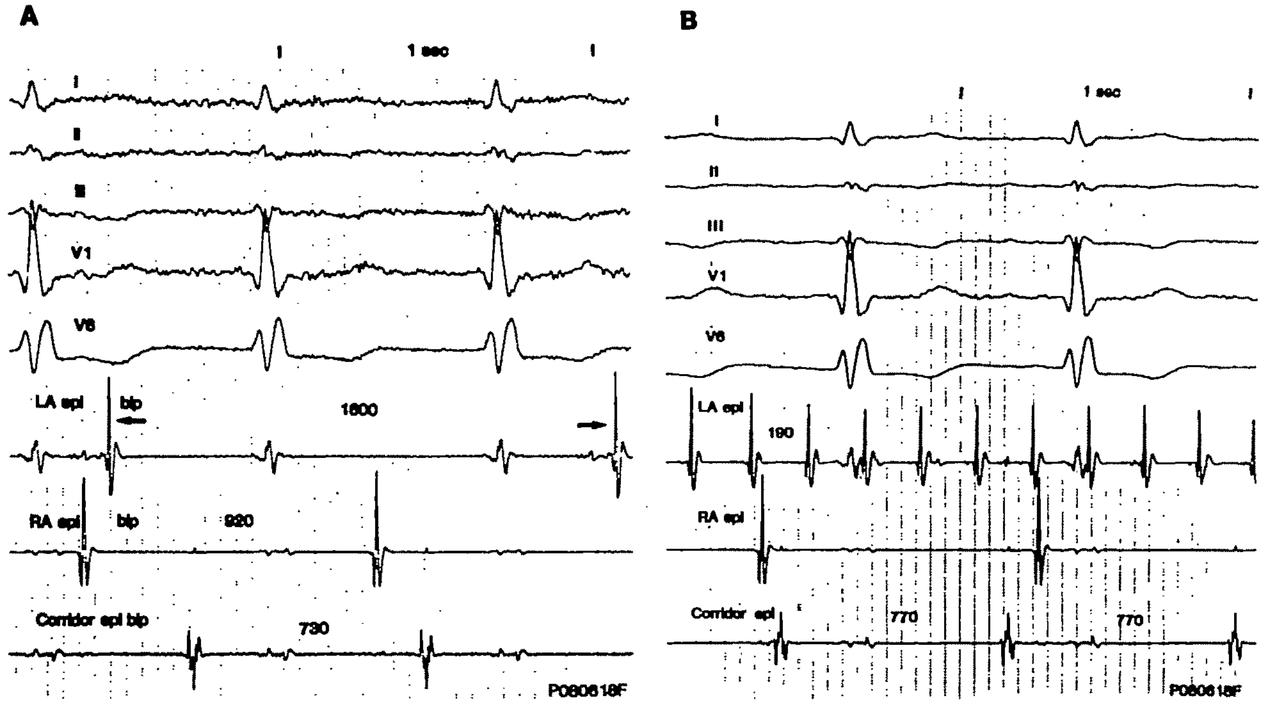

Fig 4. Results of corridor operation. Both panels show five electrocardiographic leads and the bipolar epicardial electrograms of left atrium (LA epi), *residual right* (RA epi) *and corridor* (Corridor epi) *of the same patient (paper speed, 100 mm/min). In panel (A) the left atrium shows slow rhythm (cycle length, 1,600 ms) and the residual right atrium a faster rhythm (cycle length, 920 ms), whereas the corridor has a sinus rhythm (cycle length, 730 ms) with 1:1 atrioventricular conduction and complete right bundle branch block. Panel (B) displays an atrium flutter (cycle length, 190 ms) in the left atrium. From both recordings it is evident that the sinus rhythm in the corridor is not influenced by the impulses in other compartments.*

Cardiac anatomy and function were assessed by two-dimensional echocardiography. Follow-up ended by July 1990.

Results

Preoperative Rhythm

Without antiarrhythmic drugs paroxysmal AF of a duration varying from at least 5 minutes to 48 hours was documented in all patients. In half of them cardioversion was needed to restore sinus rhythm during PES. All patients showed normal sinus node function, normal AV conduction, and absence of accessory AV pathways. Atrial fibrillation was easily induced by PES in all patients, mostly by rapid atrial stimulation. Atrial flutter, atrial focal tachycardia, and circus movement AV tachycardia were never induced at the time of PES.

Short-Term Surgical Results

Electrical isolation of the left atrium and residual right atrium was achieved in all patients at the first surgical procedure (Fig 4, see Table 1). However, in 8 patients (patients 2, 7, 9, 11, 12, 17, 18, and 20) paroxysmal fibrillation in the left atrium governing the ventricular rate reoccurred between the third and fifth postoperative day. At reoperation, carried out without extracorporeal circulation, epicardial mapping showed connection between left atrium and corridor, around or adjacent to the coronary sinus (see Fig 3). Additional dissection of the coronary sinus from the AV sulcus and extensive cryoablation of that area resulted in persistent complete isolation in 3 patients (patients 2, 7, and 11), whereas in 1 patient (patient 9) a third surgical procedure was required to obtain definitive isolation. Finally, an irregular focal arrhythmia became evident in the corridor in 1 patient (patient 15) 5 days after the initial procedure. Endocardial mapping showed that the origin of this arrhythmia was localized close to the coronary sinus, and endocardial cryoablation could suppress this arrhythmia. To summarize, a successful corridor operation was achieved in 16 of the 20 patients (80%).

However, in 4 patients the connection could not be ablated, despite reoperation. In 3 of these 4 patients (patients 12, 18, and 20) the procedure failed despite delineation of the conduction zone between left atrium and corridor at the border of the coronary sinus. In patient 20 a His bundle ablation was performed and subsequently a rate-modulated ventricular pacemaker was inserted. In 1 patient (patient 17) the site of the incomplete isolation, however, could not be detected epicardially. Consequently, cryoablation of the His bundle was performed with implantation of a rate-modulated ventricular pacemaker.

The recovery of all patients was uneventful except in 1 (patient 7), who suffered from a minor postoperative stroke on the fifth day after reoperation.

Short-Term Rhythm Observations

Repeated rhythm recordings showed normal sinus function and AV conduction in 14 of the 16 patients with a successful procedure, whereas 2 had an AV nodal escape rhythm. At successive PES, AF could never be induced in the corridor. Only 3 patients needed antiarrhythmic drugs at the time of discharge: the 2 failures (patients 12 and 18) and the patient (patient 15) with the ablated paroxysmal focal arrhythmia in the corridor to suppress this arrhythmia.

Long-Term Results

RHYTHM OBSERVATIONS. During the follow-up ranging from 7 to 37 months (mean, 20 months), the 16 patients with a successful corridor operation never had paroxysmal AF in the corridor. Three patients (patients 6, 10, and 16) had infrequent attacks of atrial flutter, which presumably arose in the corridor itself. These patients were treated with antiarrhythmic drugs. The sinus node function remained normal as evidenced during stress testing in all but 2 patients (patients 2 and 5), who could reach only 75% and 61% of the predicted heart rate. Of the 2 patients (patients 5 and 13) discharged with AV nodal rhythm, normal sinus rhythm resumed fully during follow-up in 1 (patient 13). The incidence of focal arrhythmias within the corridor (patient 15) gradually diminished as observed by successive Holter recordings.

Of the 2 patients with failed corridor procedure but without His bundle ablation, antiarrhythmic drugs could be withdrawn in 1 (patient 12) 15 months after operation because of the absence of frequent attacks of paroxysmal AF. In the other patient (patient 18), paroxysmal AF showed the preoperative frequency of AF. In this patient successful His bundle ablation was performed.

STROKE. Two patients experienced a minor stroke: five days after the reoperation in 1 (patient 7) and 4 months after discharge in the other (patient 13). In the former patient anticoagulant therapy was diminished before and started again at the first day after reoperation, and presumably therapy was still insufficient, whereas in the last patient this treatment was terminated 1 month before the event. The neurological recovery was complete within a few days in both. The echocardiographic dimension of the left atrium was normal in patient 7 and slightly enlarged in patient 13.

ECHOCARDIOGRAPHY. In none of the patients was an increase in diameter or functional deterioration of the ventricles observed during follow-up. In 6 of the 20 patients a slight increase in the diameter of the left atrium became clear compared with the preoperative studies, whereas in 1 patient (patient 8) an obvious enlargement of the left atrium occurred. In general, the right atrium did not enlarge compared with the preoperative findings. A new slight incompetence of the mitral valve was observed in 4, and of the tricuspid valve in 1 patient. Hemodynamic deterioration has not been observed.

PHYSICAL STATUS. All patients except 1 (patient 18) experienced a substantial improvement of quality of life, and all patients were able to increase physical workload.

Comment

The first surgical approach to drug-refractory AF was reported by Sealy and co-workers [4] in 1981, who used cryoablation to interrupt the His bundle. Since 1982, closed chest ablation of the His bundle with catheter electroshocks has become a widely used treatment for drug-refractory AF [3]. These procedures, however, implicate the exclusion of the physiologic cardiac pacemaker and life-long artificial pacemaker dependency. These disadvantages count more when AF arises only intermittently. The corridor operation circumvents several disadvantages of these His ablative procedures: the ventricles respond properly to changes in sinus node rhythm, which remains the best sensor for physiologic demands, and pacemaker dependency is avoided, eliminating an obvious burden to the patient. The results of the corridor operation rely on intact sinus node function, normal AV conduction, and the preoperative absence of focal arrhythmias in the portion of the right atrium of which the corridor will be constructed. Hence, in the selection of patients, sick sinus syndrome, right atrial focal tachycardia, and accessory AV bypass tracts have to be looked for and considered a contraindication.

Recurrence of conduction between the left atrium and corridor was the major problem early after operation. At reoperation, epicardial atrial mapping showed that the connection was localized exclusively around or adjacent to the proximal part of the coronary sinus in 7 of 8 patients with technical failure (Fig 5), whereas in 1 patient the site of the connection could not be found. Surviving muscle fibers running in or around the coronary sinus appear to be responsible for conduction from the left atrium to the corridor and reverse. A new series of cryoablations in this region was able to accomplish stable and complete isolation in 4 of 8 reoperated patients, without institution of extracorporeal circulation. A full transection on extracorporeal bypass followed by repair of the coronary sinus might be a solution, but was not performed in view of the risk of hemorrhagic complications, thrombosis, or cardiac venous congestion. One might expect that the problem of persistent connection could have been solved in the successive patients of this series as experience increased. However, this was not the case; hence it is apparent that this part of the operation asks for further technical refinement.

Arrhythmia emerging postoperatively in the corridor constituted a minor problem. Although spontaneous AF arising in the corridor was never observed nor could be induced (which validates the experimental concept of reduction of atrial mass to prevent AF), paroxysmal atrial

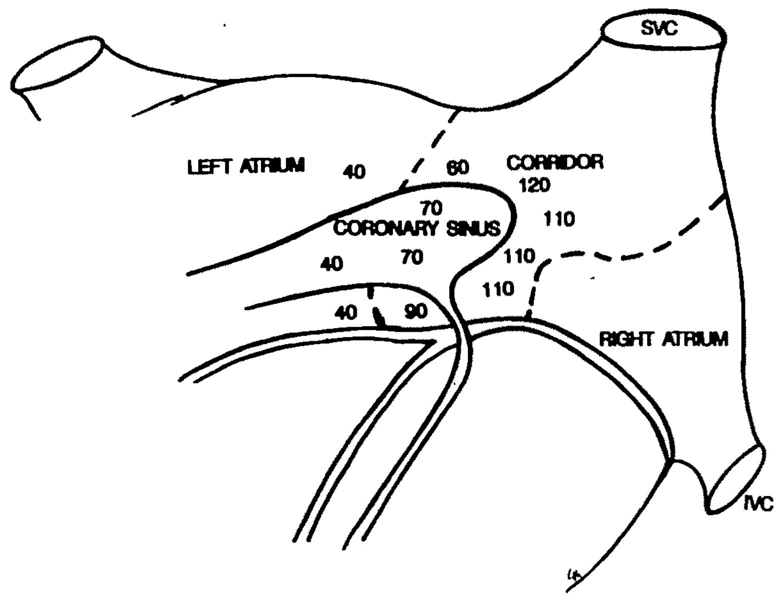

Fig 5. The surgeon's view of the posterior side of the atria with the ventricles lifted up to demonstrate the persistent electrical connection between left atrium and corridor. The figures are in milliseconds and represent the activation times during left atrial stimulation. The map shows the conduction to persist at the superior part of the coronary sinus. (*IVC = inferior vena cava;* SVC = *superior vena cava.*)

Table 2. Long-Term Results of the Corridor Operation

Patient No.	Follow-up (mo)	Complete Isolation	Basic Rhythm	New Spontaneous Arrhythmias	Antiarrhythmic Drugs at End of Follow-up	Maximal Heart Rate (beats/min)[a]	Maximal Work Load (kJ)[a]	Echocardiographic Findings at Follow-up
1	37	Yes	Sinus	...	...	127 (90)	18.0 (84)	Normal
2	37	Yes	Sinus	...	...	116 (75)	93.6 (98)	Mitral regurg 1/4
3	28	Yes	Sinus	...	...	138 (93)	93.6 (104)	Normal
4	28	Yes	Sinus	...	...	126 (80)	63.0 (77)	Normal
5	26	Yes	AV nodal	...	...	92 (61)	12.6 (42)	Slightly enlarged LA
6	26	Yes	Sinus	Atrial flutter	Flecainide	145 (92)	18.0 (49)	Slightly enlarged LA, mitral regurg 1/4
7	23	Yes	Sinus	...	...	150 (100)	54.0 (98)	Normal
8	23	Yes	Sinus	...	...	144 (100)	18.0 (74)	Slightly enlarged LA (51 mm)
9	22	Yes	Sinus	...	...	122 (85)	22.3 (98)	Slightly enlarged LA + RA, mitral regurg 1/4
10	20	Yes	Sinus	Atrial flutter	Digoxin	140 (88)	54.0 (90)	Normal
11	16	Yes	Sinus	...	...	168 (97)	270.0 (104)	Normal
12	15	No	Sinus	Atrial fibrillation	...	150 (94)	93.6 (104)	Normal
13	14	Yes	Sinus	...	...	160 (100)	72.6 (110)	Slightly enlarged LA
14	14	Yes	Sinus	...	...	153 (95)	93.6 (95)	Normal
15	13	Yes	Sinus	Tachycardia in corridor	Quinidine	161 (100)	63.0 (79)	Mitral + tricuspid regurg 1/4
16	13	Yes	Sinus	Atrial flutter	Flecainide	130 (85)	63.0 (100)	Normal
17	13	No	VVIR	...	...	151 (100)	93.6 (121)	Normal
18	8	No	Sinus	Atrial fibrillation	Flecainide	NA	NA	Normal
19	7	Yes	Sinus	...	...	141 (82)	24.0 (82)	Normal
20	7	No	VVIR	...	...	150 (94)	210.0 (105)	Normal

[a] Numbers in parentheses are percent predicted.

LA = left atrium; NA = not accessible; RA = right atrium; Regurg = regurgitation; VVIR = rate-modulated ventricular pacemaker.

flutter (3 patients) and paroxysmal focal atrial tachycardia (1 patient) arose postoperatively. Because preoperative recordings had never shown atrial flutter and PES could never induce these arrhythmias before operation in any patient, the nature of the arrhythmias remains obscure. They could be sequelae of the surgical procedure [12] or they might have been preexistent but concealed due to the dominance of paroxysmal AF. These observations emphasize the need for further investigations to define the valid indication for the corridor operation. For example, one can speculate that lone paroxysmal AF expresses an ongoing diffuse atrial disease, causing a gradual incompetence of the sinus node function in conjunction with the evolution of new atrial tachyarrhythmias such as flutter and focal tachycardia.

From serial echocardiography it appeared that the surgical procedure hardly gave rise to a dilatation of the atria. In only 1 patient could an obvious increase in the diameter of the left atrium be detected during follow-up. Until now the appearance of a slight incompetence of the mitral valve and tricuspid valve can only be explained by some dilatation of the AV annulus due to local cryoablations.

The concept and the surgical feasibility of similar isolation procedures of the left [13] and right atrium [14, 15] to treat supraventricular arrhythmias have been previously explored in dogs. Hemodynamic studies of these surgical experiments suggested that in left atrial isolation no adverse effects on ventricular function arose due to the loss of synchronous left atrial contraction [13]. This finding can be extrapolated to our surgical approach in which the left atrium is no longer activated by the sinus node and, hence, left atrial contribution to left ventricular filling is absent. This experimental observation was confirmed in our patients with successful corridor operation, in whom no hemodynamic deterioration appeared during follow-up, and the physical condition remained unimpaired as demonstrated by the results of stress testing (Table 2). This series is still too small to compare physical and mental improvement of patients with corridor operation and those with ablated His bundle and rate-modulated ventricular pacing.

Because the left atrium continues to harbor paroxysmal AF, it is not surprising that thrombus formation in the left atrium can occur after surgical isolation, leading to systemic embolism and stroke. Our observations lead us to recommend continuation of anticoagulant therapy after the corridor operation for long periods even in the absence of an enlarged left atrium.

In conclusion, these preliminary results demonstrate that the concept of the corridor operation for the surgical treatment of paroxysmal AF is valid. To be feasible, however, the operation needs surgical refinement to avoid return of conduction between left atrium and corridor. In cases of successful corridor operation (80%), follow-up could not demonstrate recurrence of paroxysmal AF nor conduction between the paroxysmally fibrillating left atrium and corridor. Conceivably, the selection of patients should be further explored to guarantee long-term reliable sinus node activity and absence of new tachyarrhythmias emerging inside the created corridor. However, when paroxysmal atrial flutter or focal tachycardia in the right atrium are documented before operation, in the future map-guided ablation of these arrhythmia can be combined with the corridor operation. Finally, an additional surgical option might be to carry out the corridor operation in patients with paroxysmal AF in whom mitral or tricuspid valve implantation or valvuloplasty are considered.

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DISCUSSION

DR JAMES L. COX (St. Louis, MO): I appreciate the opportunity of discussing this report by Dr Defauw and his colleagues, and I would especially like to thank Dr Defauw for sending me a copy of the manuscript several weeks in advance of this meeting so I would have a chance to review it. These authors, who hail from the birthplace of clinical electrophysiology, the Netherlands, have long been recognized for their many contributions to arrhythmia surgery, particularly in the area of computerized intraoperative mapping.

Certainly Dr Defauw and his colleagues are to be congratulated for accomplishing an admirable technical feat in performing the corridor procedure in 20 patients without an operative death. However, in my opinion, even the technical excellence of the authors and their demonstrated expertise in electrophysiology cannot salvage what I consider to be a fundamental conceptual fallacy of this surgical procedure.

Atrial fibrillation is an arrhythmia that has three detrimental sequelae: one is an irregular heartbeat, the second is a hemodynamic compromise because of loss of atrial kick, and the third is an increased vulnerability to thromboembolism.

As Defauw and associates correctly state, the corridor procedure surgically isolates the left atrium from the left ventricle and the right atrium from the right ventricle. Therefore it is impossible to maintain synchrony between either atrium and its respective ventricle, and as a result it cannot possibly restore hemodynamics to normal. Furthermore, because the sinus node is also isolated from both atria, the atria are free to remain electrically silent, to develop their own intrinsic rhythm, or to continue to fibrillate. Thus, the vulnerability to thromboembolism remains unchanged, a fact acknowledged by the authors in their manuscript and substantiated by the 10% incidence of stroke in their patients. Therefore, of the three detrimental sequelae of atrial fibrillation, the corridor procedure, even when completely successful, corrects only one of them, that being the irregular heartbeat.

We have employed a different approach during the past 4 years, using a technique that we have specifically designed to abolish the ability of the atrium to fibrillate while restoring a normal sinus rhythm. Because the entire atrial myocardium is activated postoperatively, the atrial transport function is preserved, more normal hemodynamics are restored, and the vulnerability to thromboembolism is abolished.

We have performed 21 operations for atrial fibrillation in the last 4 years. All 15 patients who have undergone operation and who are more than 3 months postoperative have been cured of atrial fibrillation.

Finally, in my opinion the corridor procedure can be compared with catheter ablation of the His bundle, a well-established method for accomplishing exactly the same physiologic result without opening the chest. Like the corridor procedure, catheter ablation of the His bundle does nothing to restore the atrial kick or to decrease the likelihood of thromboembolism, but it does restore the regular heartbeat, albeit with the aid of a permanent pacemaker. Thus, the only demonstrable or theoretical advantage of the corridor procedure over catheter ablation of the His bundle for atrial fibrillation would appear to be the avoidance of a permanent pacemaker. All other physiologic results of the two forms of treatment are the same.

Therefore, my only question for Dr Defauw is, in what situation do you recommend the corridor procedure in place of catheter ablation of the His bundle for atrial fibrillation, and why do you recommend it?

DR DEFAUW: Thank you very much, Dr Cox, for your comments and the data showing your approach for the surgical therapy for atrial fibrillation.

As regards your question about which patients we would recommend for the corridor operation, it is our opinion that pacemaker dependency is a rather hard burden to bear for patients, especially for relatively young patients under 50 years of age. Therefore we select patients with poor sinus node function or classic sick-sinus syndrome for His bundle ablation, and in case of normal sinus node function we prefer the corridor procedure. It remains undisputable that the sinus node is the best sensor for ventricular pacing. In spite of loss of left atrial transport for ventricular filling, we believe that the corridor procedure is better than ablation of the His bundle because the best physiological pacing remains available.

As regards the stroke incidence in these patients, due to the loss of atrial synchrony, the risk of embolus formation is very comparable between the corridor patients and the patients with ablated His bundle. After our initial experience, we are convinced that anticoagulant therapy in these cases is beneficial to prevent thromboembolic complications.

Noninvasive Detection of Heart Transplant Rejection With Positron Emission Scintigraphy

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Positron emission tomography has recently been used to evaluate ischemic heart disease through changes in myocardial blood flow and carbohydrate metabolism. Positron-emitting tracers were evaluated for their ability to detect acute allograft rejection after heterotopic cardiac transplantation in the rat. Sham-operated controls, nonrejecting isografts, and rejecting allografts were evaluated. Decay-corrected uptake of $^{13}NH_3$ and ^{18}F 2-fluoro 2-deoxyglucose (FDG) reflects blood flow and glucose flux, respectively. Histologic examination of rejecting allografts documented mild rejection at 4 days and severe acute rejection by 8 days. All isografts were free from rejection. Uptake of FDG is greater in rejecting allografts than in nonrejecting isografts during both severe rejection (2.4% ± 0.8% versus 0.7% ± 0.4%; $p < 0.02$) and mild rejection (2.1% ± 0.6% versus 0.4% ± 0.1%; $p < 0.02$). Uptake of NH_3 in severely rejected grafts is reduced compared with nonrejecting grafts (0.6% ± 0.3% versus 1.7% ± 1.1%; $p < 0.02$). There is no difference in NH_3 uptake during mild rejection (1.8% ± 0.7% versus 1.3% ± 0.3%; $p > 0.05$). Uptake of FDG and NH_3 in native hearts of animals from all experimental groups is not significantly different from that in sham-operated controls. Glucose may be a preferred metabolic substrate during rejection. Our data support a humoral mechanism for substrate preference during transplant rejection and a potential diagnostic role for positron emission tomography.

(Ann Thorac Surg 1992;53:572–7)

The search for a reliable noninvasive method to assess allograft rejection after cardiac transplantation has been the subject of previous investigations. Endomyocardial biopsy remains the standard in the diagnosis of cardiac allograft rejection, but its invasive nature and the possibility of sampling error remain problematic [1]. Various nuclear imaging modalities (gated blood pool imaging [2], indium-111–labeled leukocytes [3, 4], and antimyosin Fab fragments [5, 6]), electrocardiographic voltage changes [7], echocardiography [8, 9], and magnetic resonance imaging [10–12] have all been proposed as adjuncts to biopsy in identifying allograft rejection. No method has yet proved to be adequately sensitive and specific to be clinically applicable. Positron emission tomography (PET) is a relatively new imaging modality that has gained attention for its ability to provide accurate information regarding tissue metabolism and blood flow.

By using specific physiologic substrates prepared with positron-emitting isotopes, PET can assess various metabolic processes in the heart [13]. Radiopharmaceutical tracers available for metabolic and flow studies with PET are listed in Table 1. The agent used most commonly for metabolic studies is glucose that has undergone substitution of fluorine 18 for oxygen at its 2-carbon position. This ^{18}F 2-fluoro 2-deoxyglucose (FDG) competes with glucose for facilitated transport into myocardial cells, where it is phosphorylated. The phosphorylated form of the tracer cannot be utilized in physiologic processes, is relatively impermeable to cell membranes, and is therefore "trapped" in the cell. Uptake of FDG measured by PET is proportional to glucose utilization in the tissue. Dynamic PET imaging with a tracer kinetic model has verified the ability of FDG and PET to noninvasively measure myocardial glucose utilization in dogs [14] and in humans [15].

^{13}N ammonia (NH_3) is one of several agents actively extracted by the myocardium and distributed in proportion to blood flow. It is metabolically trapped in the myocardium in concentrations proportional to microsphere blood flow measurements over a normal physiological range of flows (0.4 to 2.5 $mL \cdot min^{-1} \cdot g^{-1}$) [13].

Whereas the principal applications of PET in cardiac imaging have been in the evaluation of patients with ischemic heart disease [16], we sought to determine whether we could detect changes in myocardial metabolism and blood flow associated with acute graft rejection after experimental cardiac transplantation using positron-emitting tracers. Because of the limited resolution of PET

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Table 1. Radiopharmaceutical Tracers Available for Positron Emission Tomography

Tracer	Pathway	$T_{1/2}$ (min)
Metabolism		
^{18}F deoxyglucose	Glucose metabolism	109.7
^{11}C acetate	Oxidative phosphorylation	20.4
^{11}C palmitate	Fatty acid oxidation	20.4
Blood flow		
^{13}N ammonia	Myocardial blood flow	9.8
^{15}O water	Myocardial blood flow	2.1
^{82}Rb rubidium	Myocardial blood flow	1.25

$T_{1/2}$ = half-life.

and the size of hearts to be studied, scintigraphy was chosen over tomography to document these changes.

Material and Methods

Inbred male Lewis rats weighing 150 to 200 g were used as recipients in all cases. Male Lewis and F1 generation Lewis × Brown Norway rats of similar size were used as donors. Animals were anesthetized with intraperitoneal pentobarbital, 50 mg/kg, and supplemented with 10 to 20 mg/kg as needed. Heterotopic cardiac transplantation was performed according to the method of Ono and Lindsay [17] as refined by Areneda and colleagues [18]. Myocardial protection was optimized by a single aortic root injection of cold (4°C) crystalloid and topical hypothermia at the time of harvest.

All animals received humane care in compliance with the Animal Welfare Act of 1985 (amended 1989) as outlined in the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (DHEW [NIH] publication No. 85-23, revised 1985).

Study Design

Rats were divided into six experimental groups (Table 2). Group C is sham-operated controls, which underwent laparotomy and aortic cross-clamping but did not receive a graft. Group N, nonrejecting isografts, were Lewis rats that received a heterotopic cardiac isograft from a Lewis donor. Group R, rejecting allografts, were Lewis rats that received an allograft from an F1 generation Lewis × Brown-Norway donor.

No immunosuppressive agents were given. Animals were monitored daily for graft viability by palpation of the graft. Mild acute histologic rejection was reproducibly present in the allografts on postoperative day 4. Severe rejection was defined as the cessation of palpable contractions in the grafted heart. This occurred reliably in the allografts by the eighth postoperative day. At the conclusion of all experiments, grafted and native hearts were formalin-fixed and examined histologically. Rejection was graded according to the criteria of Billingham [19].

Table 2. Experimental Groups

Group	Graft	Donor	Recipient
C_1	Sham-operated control 8 day	None	LEW
C_2	Sham-operated control 4 day	None	LEW
N_1	Nonrejecting isograft 8 day	LEW	LEW
N_2	Nonrejecting isograft 4 day	LEW	LEW
R_1	Rejecting allograft 8 day	LBN	LEW
R_2	Rejecting allograft 4 day	LBN	LEW

LBN = Lewis × Brown-Norway; LEW = Lewis.

Positron Emission Scintigraphy

Animals to be studied by positron emission scintillation counting were subjected to the following schedule (Table 3). After generation of positron-emitting radiopharmaceuticals FDG and NH$_3$ in the cyclotron, three 10-μL samples of each were placed in scintillation vials and counted for 60 seconds each both shortly after generation and at time 3. Isotopes were eluted from the cyclotron in sterile water and made isotonic by addition of 23.4% NaCl. One hundred microcuries of FDG was injected through the tail vein at time 0 and 200 μCi of NH$_3$ was injected 35 minutes later. Adequacy of injection was ensured using a standard Geiger counter. Sacrifice was accomplished by decapitation 45 minutes after FDG injection. A blood sample was collected in a heparinized tube and the grafted and native hearts were rapidly excised and rinsed in cold normal saline solution. A biopsy sample of the left ventricular free wall at the apex was taken. Extraneous great vessel and atrial tissue was trimmed. The hearts were dried, weighed to an accuracy of 0.0001 g (Mettlar), and placed in scintillation vials. Grafted and native hearts were counted in a standard scintillation counter (Pharmaciae LKB Nuclear) for 60 seconds at time points 1, 2, and 3 (50, 60, and 180 minutes after FDG injection).

Data Analysis

The following strategy was used to determine metabolic and blood flow data from the radioactive counts (Table 4). Because the half-life of FDG (110 minutes) is much longer than that of NH$_3$ (10 minutes), counts obtained at times 1 and 2 are a combination of FDG and NH$_3$ activity. By time 3, greater than 99% of the ammonia has decayed and

Table 3. Experimental Protocol

Time (min)	Protocol
0	FDG Injected
35	NH$_3$ Injected
45	Sacrifice
50	Time 1 counts measured
60	Time 2 counts measured
180	Time 3 counts measured

FDG = ^{18}F 2-fluoro 2-deoxyglucose; NH$_3$ = ^{13}N ammonia.

Table 4. Abbreviations Used in Formulas

Measurement	FDG Injection	NH_3 Injection	Time 1	Time 2	Time 3	Control
Time	tF	tN	t1	t2	t3	tC
Counts	. . .	. . .	C1	C2	C3	CC

FDG = ^{18}F 2-fluoro 2-deoxyglucose; NH_3 = ^{13}N ammonia.

remaining radioactivity represents FDG activity alone. Counts at time 3 are decay-corrected with the following formula:

$$Ao = C3\ e^{\ln 2(t3 - tF)/110\ \text{min}}$$

This value is then divided by the product of the weight of the heart and the injected dose of FDG and represents glucose metabolism in the tissue, expressed as the percent uptake of FDG per gram of tissue (CC FDG = radioactive count from known standard of FDG):

$$FDG = (Ao)/[\text{Weight (g)} \times CC\ FDG \times e^{2\ln 2(t1 - tF/110)}]$$

To determine blood flow information, radioactive counts at times 1 and 2 are corrected to reflect NH_3 by subtracting the fraction contributed by FDG from the total according to the following equations:

$$N1 = C1 - Ao\ e^{-\ln 2(t1 - tN)/110}$$

$$N2 = C2 - Ao\ e^{-\ln 2(t1 - tN)/110}$$

These values are then decay corrected:

$$N1^* = N1\ e^{\ln 2(t1 - tN)/10\ \text{min.}}$$

The decay-corrected values, ie N1*, are divided by the product of the weight of the tissue and the injected dose of NH_3 and reflect blood flow in the tissue expressed as the percent uptake of NH_3 per gram of tissue (CC NH_3 = radioactive count from known standard of NH_3):

$$Flow = N1^*/[\text{Weight (g)} \times CC\ NH_3 \times e^{\ln 2(t1 - tc)/10}]$$

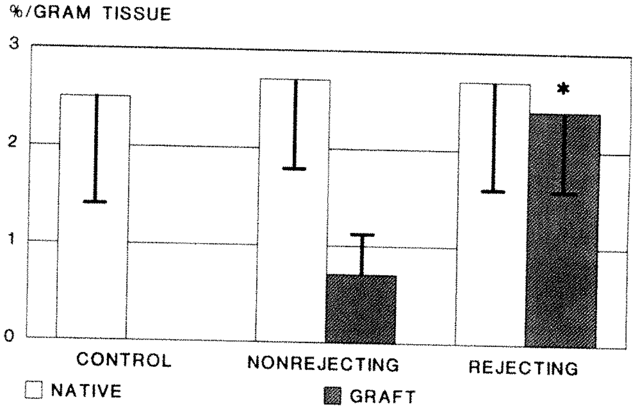

*Fig 1. Uptake of FDG on postoperative day 8 in hearts of sham-operated controls and in native and grafted hearts with no rejection (isografts) and severe acute rejection (allografts). (*p < 0.02 versus nonrejecting.)*

Statistical analysis was performed using analysis of variance and Student's *t* test, with the level of statistical significance set at $p = 0.05$.

Results

The initial phase of this experimental investigation involved allografts undergoing severe rejection. Recipients were divided into three groups (Fig 1). Table 5 shows the number of animals studied in each group. No difference among groups were observed with regard to graft ischemia time, total operative time, or postoperative day of study (Table 6). In the group with severe acute rejection, FDG uptake in the allografts was significantly higher than in nonrejecting isografts ($p < 0.001$) (see Fig 1). Uptake of FDG in native hearts from either operated group was not statistically different from that in sham-operated control animals ($p = 0.816$ versus nonrejecting, $p = 0.791$ versus rejecting). Uptake of NH_3 in the severely rejected grafts was significantly lower than in nonrejecting grafts ($p < 0.02$) (Fig 2). Uptake of NH_3 in the native hearts of those

Table 5. Experimental Results[a]

Group	n	NH_3 Uptake		FDG Uptake	
		Graft	Native	Graft	Native
Control					
C_1	11	. . .	1.1 ± 0.2	. . .	2.5 ± 1.1
C_2	10	. . .	1.2 ± 0.5	. . .	2.4 ± 0.6
Mild rejection					
N_2 nonrejecting	11	1.3 ± 0.3	1.2 ± 0.5	0.4 ± 0.1	2.3 ± 0.9
R_2 rejecting	11	1.8 ± 0.7[b]	1.1 ± 0.6	2.1 ± 0.6[c]	1.9 ± 0.5
Severe rejection					
N_1 nonrejecting	12	1.7 ± 1.1	1.3 ± 0.8	0.7 ± 0.4	2.7 ± 0.9
R_1 rejecting	11	0.6 ± 0.3[c]	1.2 ± 0.3	2.4 ± 0.8[c]	2.7 ± 1.1

[a] Values are percent of injected dose per gram of tissue ± standard deviation. [b] $p < 0.01$ versus control. [c] $p < 0.02$ versus nonrejecting.
FDG = ^{18}F 2-fluoro 2-deoxyglucose; NH_3 = ^{13}N ammonia.

Table 6. Operative Data

Variable	Sham-Operated Controls	Nonrejecting Isograft	Rejecting Allograft
Ischemic time (min)	. . .	17.3	17.2
Operative time (min)	40.0	41.3	39.4
Postoperative day studied	8.0	7.3	8.0

animals from each experimental group was not significantly different from control ($p = 0.948$ versus nonrejecting, $p = 0.500$ versus rejecting).

Histologic examination of these severely rejected hearts revealed an intense homogeneous perivascular and interstitial cellular infiltrate with diffuse areas of myocyte necrosis consistent with severe acute rejection (Fig 3). Histologic examination of all isografts, sham-operated controls, and native hearts showed no evidence of rejection.

During the second phase of the investigation, we evaluated less severe rejection to determine whether the decrease in NH_3 uptake (decrease in blood flow) seen in severe rejection may have itself affected glucose uptake. We observed that mild rejection was seen histologically 4 days after transplantation. Figure 4 shows a photomicrograph from a biopsy specimen of a heart 4 days postoperatively and demonstrates minimal perivascular leukocyte infiltration without major interstitial infiltrates or evidence of myocyte necrosis, the typical changes of mild acute rejection [19]. No evidence of rejection was seen in any isograft, control, or native heart. Table 5 illustrates the number of animals from each experimental group that were studied at 4 days postoperatively. Again, no difference was observed among these groups with regard to graft ischemia time, total operative time, or postoperative day of study. With regard to FDG uptake during mild rejection, a pattern similar to that observed with severe rejection emerged: FDG uptake in allografts undergoing mild rejection was significantly higher than that in nonrejecting isografts ($p < 0.01$) (Fig 5). Ammonia uptake of mildly rejecting allografts approached that of nonrejecting isografts but failed to reach statistical significance ($p = 0.056$) (Fig 6).

Comment

Positron emission scintigraphy detects changes in the uptake of NH_3 and FDG representing blood flow and glucose flux, respectively, during acute allograft rejection using a model of heterotopic heart transplantation in the rat. Our data suggest that glucose flux increases during both severe and mild acute rejection. Although this increase in glucose utilization may have been secondary to diminished perfusion during severe rejection, similar changes were confirmed during mild rejection. We postulate that this phenomenon may be explained by a change in the preferred metabolic substrate in the heart (from fatty acids to glucose) during rejection.

Blood flow was reduced in severe acute rejection and not in mild rejection. Therefore, it appears that the

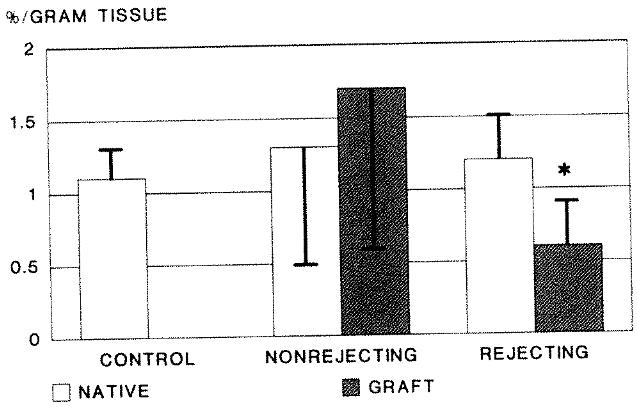

Fig 2. Uptake of NH_3 on postoperative day 8 in hearts of sham-operated controls and in native and grafted hearts with no rejection (isografts) and severe acute rejection (allografts). ($p < 0.02$ versus nonrejecting.)*

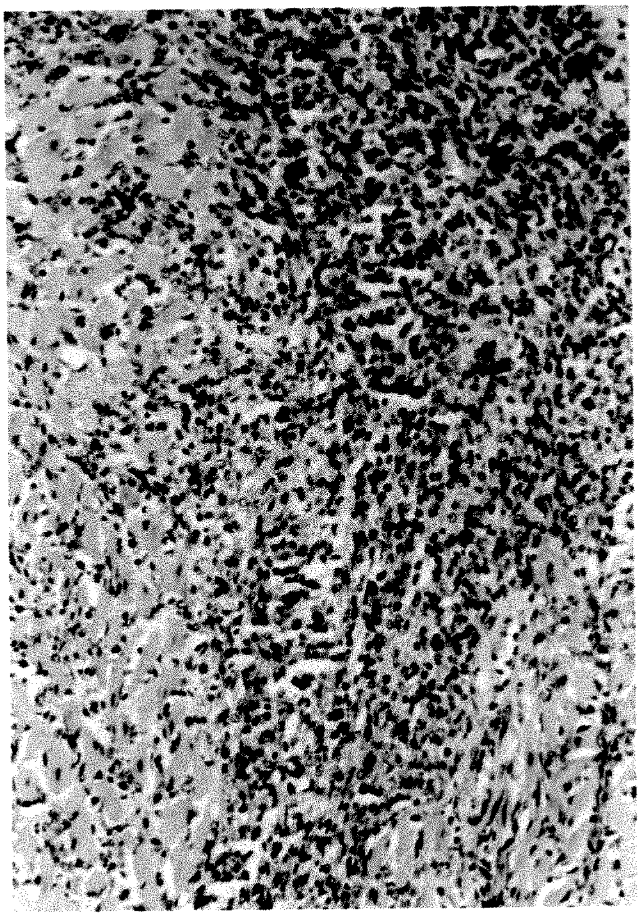

Fig 3. Photomicrograph demonstrating severe acute cardiac rejection on postoperative day 8. (Hematoxylin and eosin; ×230 before 28% reduction.)

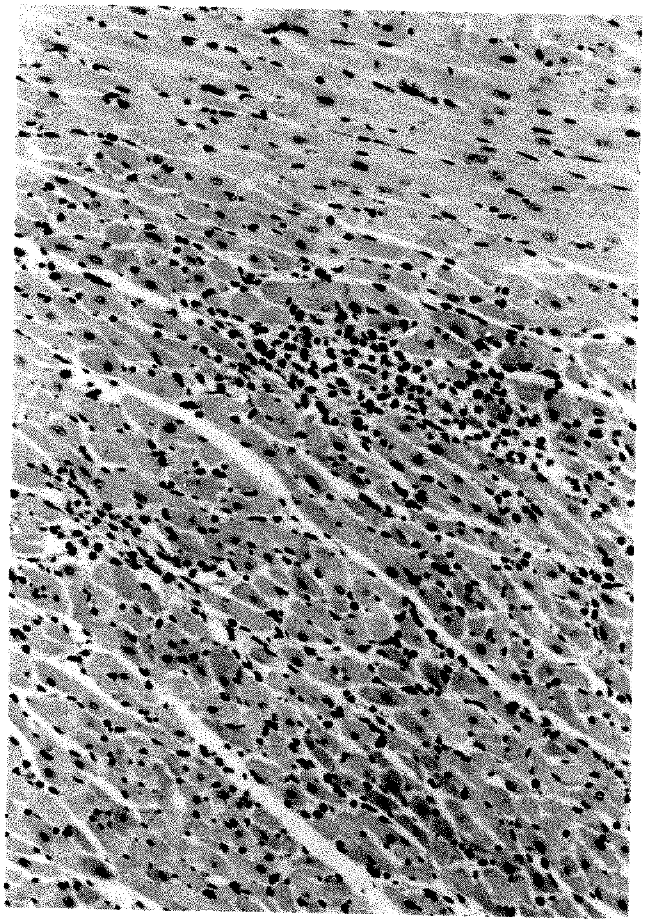

Fig 4. Photomicrograph demonstrating mild acute cardiac rejection on postoperative day 4. (Hematoxylin and eosin; ×230 before 28% reduction.)

changes in FDG uptake (and, by inference, metabolic substrate) are independent of blood flow. These data suggest a potential humoral mechanism for the metabolic state of the heart in the setting of acute rejection.

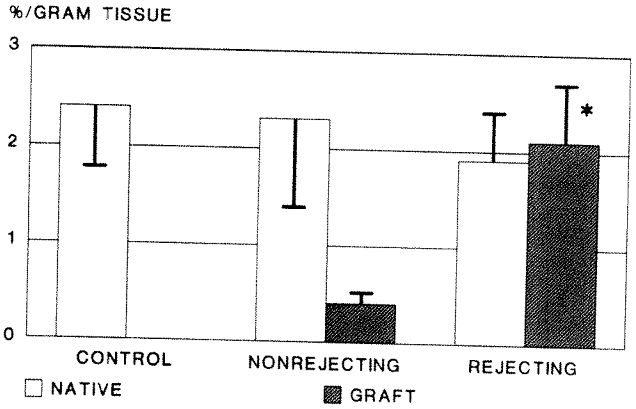

*Fig 5. Uptake of FDG on postoperative day 4 in hearts of sham-operated controls and in native and grafted hearts with no rejection (isografts) and mild acute rejection (allografts). (*p < 0.02 versus nonrejecting.)*

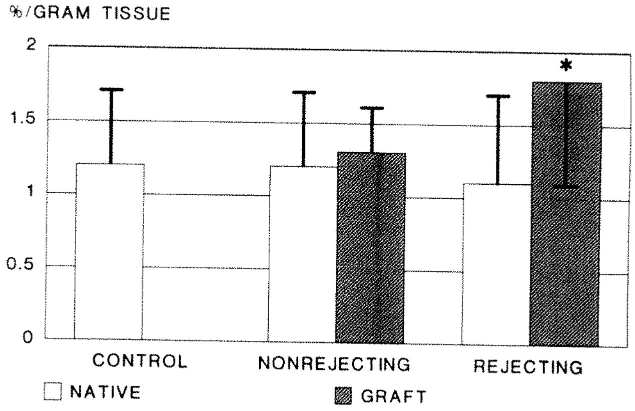

*Fig 6. Uptake of NH_3 on postoperative day 4 in hearts of sham-operated controls and in native and grafted hearts with no rejection (isografts) and mild acute rejection (allografts). (*p < 0.01 versus control.)*

Mechanisms leading to the metabolic changes that we have observed during acute rejection remain to be elucidated. This may be an expression of the oxidative state of the myocardium or the consequence of released humoral factors such as cytokines, lymphokines, or growth factors. The contribution of leukocyte metabolism, if any, may also bear further investigation. However, it is interesting to us that FDG uptake was actually greater in the mildly rejecting hearts, as compared with severely rejecting hearts, making it very unlikely that leukocytes contributed significantly to the changes noted in FDG uptake.

Endomyocardial biopsy is the standard against which all diagnostic modalities of rejection have been judged. Using the technology available today, evaluation of five biopsy specimens has a false-negative rate of approximately 2% [20]. Grading of acute rejection is well described [19]. These systems are based on the detection of the cellular elements of rejection seen on histologic section. With its ability to evaluate metabolic changes, PET offers the unique potential of diagnosing rejection before a cellular response develops, with concomitant vascular and myocyte injury.

Ultimately, correlation with histopathologic evidence of rejection should help determine whether this noninvasive modality may be used in the future either to supplement or replace the information currently obtained by endomyocardial biopsy in detecting treatable cardiac allograft rejection.

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DISCUSSION

DR VERDI J. DISESA (Philadelphia, PA): This is a very nicely done study. I think that the heterotopic rat model is really very useful for studying a number of questions related to heart transplantation.

You describe an increase in glucose metabolism, at least glucose uptake, with rejection, but what you do not comment on but which is equally striking to me was the significant decrease in glucose uptake in the nonrejecting isografts. Presumably this is a consequence of denervation, but have you looked into what the mechanism of that might be? Might that be another fruitful way to get a handle on what is going on with the metabolic changes in these grafts?

DR HOFF: In analyzing these data, we were also taken by the decrease in glucose metabolism that we noted in the nonrejecting isografts and have attempted to work out the exact etiology. One potential mechanism that we have evaluated is the nonworking nature of this model. As you mentioned, this has been a model that has been used for years for basic and important research in the treatment of heart transplant rejection, but its limitations are that it truly is a nonworking model.

We have developed fairly recently in our laboratory a modification of this model that allows the heterotopically transplanted heart to work; our preliminary data suggest that the decrease in glucose metabolism that we have noted in these isografts may be a consequence of the nonworking nature of this model, and that further studies may need to be done with this working model to elucidate changes with allograft rejection.

DR W. STEVES RING (Dallas, TX): My colleagues and I really have no experience with PET scanning for the diagnosis of cardiac rejection. Our work has been primarily with magnetic resonance imaging scans, where prolongation of the T_2 relaxation time seems to correlate well with histologic evidence for rejection. Positron emission tomographic scanning should be quite helpful in our understanding of the metabolic processes associated with rejection. However, although these technologies may be quite useful from a research standpoint, we have found that their cost will probably limit their clinical application for surveillance of cardiac rejection after transplantation.

Effect of Pulmonary Resection on Right Ventricular Function

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The effect of pulmonary resection on right ventricular (RV) performance and its possible contribution to morbidity or mortality remain unclear. Using thermodilution methods and a fast-response thermistor positioned in the pulmonary artery, it is now possible to measure RV end-diastolic volume and RV ejection fraction. Using this technique, RV performance during and after major pulmonary resection was studied in 15 patients. Significant RV dysfunction was demonstrated in the postoperative period. Right ventricular end-diastolic volume increased significantly on postoperative day 1 (177 ± 9 mL) and postoperative day 2 (172 ± 4 mL) versus early postoperatively (153 ± 10 mL) ($p < 0.05$). By postoperative day 2, RV ejection fraction was significantly decreased (0.36 ± 0.03) from preoperative (0.45 ± 0.02) and early postoperative (0.40 ± 0.01) values ($p < 0.05$). Although pulmonary artery pressures rose modestly in the postoperative period, and pulmonary vascular resistance increased by postoperative day 2, pulmonary vascular resistance remained significantly lower or unchanged from baseline values. We speculate that the etiology of the RV dysfunction after pulmonary resection may be multifactorial. Changes in RV afterload or alteration in RV contractility may be factors.

(Ann Thorac Surg 1992;53:578–82)

Thermodilution has been successfully used to measure right ventricular (RV) performance after coronary artery bypass grafting and in patients with sepsis, shock, and thermal injury [1–3]. Major RV dysfunction has been correlated with poor outcome and implicated in the pathophysiology of the event. Changes in RV function after pulmonary resection are unknown. The RV thermodilution ejection fraction/volumetric catheter allows assessment of changes in RV performance during and after major pulmonary resection. This study was undertaken (1) to validate our preliminary observations that RV function changes significantly after major pulmonary resection and suggests RV dysfunction, (2) to assess duration of RV dysfunction and its relation to preload and pulmonary hemodynamics, and (3) to develop hypotheses regarding the mechanisms for RV dysfunction.

Material and Methods

Patient Population

Fifteen patients undergoing either lobectomy or pneumonectomy at the Medical University of South Carolina Medical Center or the Charleston VA Hospital underwent placement of the RV thermodilution ejection fraction/volumetric catheter before induction of anesthesia. Informed consent procedure approved by the Institutional Human Review Board was used. The 15 patients consisted of 12 men and 3 women with a mean age of 65 ± 1.8 years (range, 44 to 77 years). None of the patients had symptomatic coronary artery disease, valvular heart disease, or atrial arrhythmias. No patient routinely used cardiac medications other than antihypertensive agents (7 patients). All patients had unremarkable cardiac examinations. To ensure that physical assessment did not miss any important tricuspid regurgitation, which may have affected thermodilution measurements, 5 patients underwent preoperative echocardiography. Tricuspid regurgitation was not found in any patient. Catheter-induced tricuspid regurgitation has been shown to be small and unlikely to be important in the assessment of thermodilution cardiac output [4]. The majority of the patients had chronic obstructive lung disease with a mean forced expiratory volume in 1 second of 1.96 ± 0.62 L/min. Resections included 8 left upper lobectomies, 1 left lower lobectomy, 4 right lower lobectomies, and 2 left pneumonectomies. All patients underwent intubation with a double-lumen endotracheal tube and insertion of radial arterial catheters for constant blood pressure monitoring. Chest tubes were placed in the pleural cavity after resection and remained at −20 cm H_2O suction during the remainder of the study period.

Thermodilution Measurements and Computations

A multilumen thermodilution catheter mounted with a rapid-response thermistor (7.5F; Baxter Healthcare Corp, Irvine, CA) was positioned 3 to 4 cm distal to the pulmonic valve. The output from this thermistor as well as the analog electrocardiographic signal were interfaced to a thermodilution ejection fraction computer (REF-1; Baxter Healthcare Corp). Using this catheter and computer system, RV ejection fraction (RVEF), cardiac output, and RV end-diastolic volume (RVEDV) were computed from the thermodilution curve as previously described [5–7]. Briefly, a 10-mL bolus of 5% dextrose (3°C) was injected into the right atrium over 3 seconds. The subsequent temperature changes within the pulmonary artery were

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Table 1. Intraoperative Measurements[a]

Data Interval	HR (beats/min)	MAP (mm Hg)	CVP (cm H_2O)	PAP_S (mm Hg)	PAP_D (mm Hg)	MPAP (mm Hg)	CO (L/min)	RVEDV (mL)	RVEF	PVR (mm Hg/s)
Baseline: supine, awake	72 ± 3	101 ± 3	6 ± 1	31 ± 2	13 ± 1	20 ± 1	4.91 ± 0.26	157 ± 8	0.45 ± 0.02	116 ± 11
Chest open	70 ± 3	93 ± 4	9 ± 1	33 ± 2	17 ± 2	23 ± 2	4.86 ± 0.24	168 ± 7	0.44 ± 0.01	113 ± 12
PA ½ occluded	67 ± 4	86 ± 4	3 ± 1	31 ± 2	15 ± 1	22 ± 1	4.47 ± 0.24	160 ± 6	0.44 ± 0.02	115 ± 12
PA occluded	65 ± 4	86 ± 2	3 ± 1	37 ± 2[b]	16 ± 1	24 ± 1	4.48 ± 0.24[b]	164 ± 10	0.43 ± 0.02	150 ± 12[b]
Resection completed	72 ± 2	85 ± 3	4 ± 1	32 ± 3	15 ± 1	22 ± 2	4.85 ± 0.29	166 ± 11	0.43 ± 0.02	116 ± 8
Supine closed	72 ± 3	88 ± 4	3 ± 1	34 ± 3	16 ± 1	24 ± 2	4.44 ± 0.33[b]	144 ± 8	0.43 ± 0.02	141 ± 9[b]

[a] Number of patients = 15. Values are means ± standard error. [b] Indicates significant difference from baseline, $p < 0.05$.

CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PAP_D = pulmonary artery diastolic pressure; PAP_S = pulmonary artery systolic pressure; PVR = pulmonary vascular resistance; RVEDV = right ventricular end distolic volume; RVEF = right ventricular ejection fraction.

acquired by the computer and approximated as an exponential decay process [5–7]. From the exponential function, the rate of temperature decay between two successive RV contractions was computed [5–8]. This rate of temperature change was then transformed to an ejection fraction. Cardiac output was determined by computing the area under the thermodilution curve, as described previously [9]. Right ventricular stroke volume was computed as the quotient of cardiac output and heart rate. Right ventricular end-diastolic volume was computed as the quotient of RV stroke volume and RVEF.

The position of the fast-response thermistor was maintained throughout the study at 3 to 4 cm from the pulmonic valve. This distance was carefully controlled because it has been reported previously that excessive distances from the pulmonic valve can result in attenuated thermodilution ejection fraction measurements [8]. Maintaining this thermistor distance prevented us from obtaining reliable pulmonary capillary wedge pressures at all times of data collection. However, initial pulmonary capillary wedge pressures correlated with pulmonary artery diastolic pressures within 1 to 2 mm Hg. Accordingly, the pulmonary artery diastolic pressure was used as an approximation of pulmonary capillary wedge pressure and in the calculation of pulmonary vascular resistance.

Before induction of anesthesia, the following measurements were obtained: heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure (PAP), mean pulmonary artery pressure, cardiac output, RVEDV, and RVEF. These measurements were repeated when the chest was open, the main branch pulmonary artery approximately half occluded and totally occluded for left-sided resections, at the completion of resection with the chest open, before transport to the intensive care unit, 4 to 6 hours postoperatively, on postoperative day (POD) 1, and on POD 2.

The criteria for obtaining satisfactory thermodilution computations were that the thermodilution curve approximated an exponential decay process and that the electrocardiographic signal was properly acquired during the thermodilution measurement. A triplicate set of thermodilution measurements meeting these criteria were obtained at each time point.

Statistical Analysis

Hemodynamic measurements and indices of RV function were compared at the various time points using multiway analysis of variance. Pairwise tests of individual group means were compared using the paired *t* test [10].

Results

The intraoperative measurements (Table 1) showed no significant changes with the exception of an increase in pulmonary vascular resistance (PVR) and pulmonary artery systolic pressures when the left main branch pulmonary artery was occluded. Despite total occlusion of this artery, there were no acute changes in either RVEF or RVEDV.

Measurements in the postoperative period are summarized in Table 2. In the early postoperative period, PAP decreased. Pulmonary artery pressure returned to baseline values on POD 1 and 2. This increase in postoperative PAP was significantly different from early postoperative values ($p < 0.05$) (Fig 1). In all postoperative periods, PVR remained lower than at baseline and was significantly reduced early postoperatively and on POD 1 ($p < 0.05$) (Fig 2).

In the early postoperative period (4 to 6 hours), RVEF significantly declined below baseline despite decreases in PAP and PVR. On POD 1 and 2, RVEF remained depressed, and by POD 2 it declined below both baseline and early postoperative values ($p < 0.05$) (Fig 3). There was significant RV dilatation on POD 1 and 2 compared with the early postoperative period ($p < 0.05$), which accompanied the continued depression in RVEF (Fig 4).

Central venous pressure was unaltered over time. Indices of left ventricular function, ie, cardiac output and mean arterial pressure, were maintained in the postoperative period.

Three patients had periods of sustained atrial arrhythmias on POD 1 or 2 and at the time had significant increases in RVEDV. There was no operative mortality.

Table 2. Postoperative Measurements[a]

Data Interval	HR (beats/min)	MAP (mm Hg)	CVP (cm H_2O)	PAP_S (mm Hg)	PAP_D (mm Hg)	MPAP (mm Hg)	CO (L/min)	RVEDV (mL)	RVEF	PVR (mm Hg/s)
4 to 6 h postop	90 ± 4^b	81 ± 3^b	6 ± 1	26 ± 2	13 ± 1	19 ± 2	5.36 ± 0.10	153 ± 10	0.40 ± 0.01^b	85 ± 11^b
POD 1	90 ± 3^b	81 ± 3^b	6 ± 1	33 ± 3^c	16 ± 1^c	22 ± 2^c	$6.41 \pm 0.33^{b,c}$	177 ± 9^c	0.41 ± 0.02	81 ± 10^b
POD 2	96 ± 5^b	86 ± 5	5 ± 1	34 ± 3^c	15 ± 1^c	22 ± 2^c	$5.70 \pm 0.24^{b,c}$	173 ± 14^c	$0.36 \pm 0.03^{b,c}$	104 ± 14^c

[a] Number of patients = 15. Values are means ± standard error. [b] Indicates significant difference from baseline, $p < 0.05$. [c] Indicates significant difference from 4 to 6 h postop value, $p < 0.05$.

CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PAP_D = pulmonary artery diastolic pressure; PAP_S = pulmonary artery systolic pressure; POD = postoperative day; PVR = pulmonary vascular resistance; RVEDV = right ventricular end distolic volume; RVEF = right ventricular ejection fraction.

Comment

We have demonstrated that there is significant RV dilatation indicative of RV dysfunction after routine pulmonary resection. Right ventricular end-diastolic volume increased on POD 1 and 2, and by POD 2, RVEF was significantly decreased from preoperative baseline values and from the early postoperative period.

In the present study, attempts were made to assess the effects of RV afterload intraoperatively. Interestingly, acute changes in RV afterload had minimal immediate effect on RVEF and RVEDV. In the early postoperative period, there was a significant decline in RVEF despite a reduction in PVR and PAP, two indicators of RV afterload. Thus the change in RVEF was independent of any change in afterload. By the first postoperative day, PAP had returned to baseline values. However, PVR remained significantly lower than baseline. Right ventricular ejection fraction remained decreased on POD 1 and further declined on POD 2. Concomitant with this decreased pump performance was noteworthy RV dilatation.

It is known that the right ventricle is sensitive to changes in afterload because of its small muscle mass. With increased afterload, RVEF decreases [11–14]. Over a wide range of preload, there is a decrease in systolic shortening as a function of end-diastolic length, which corresponds to the decrease in RVEF observed with elevated afterload [15]. The ability of the right ventricle to maintain stroke volume in the face of increased afterload is dependent on the ability to augment end-diastolic volume. However, although increased afterload may be important in the development of RV dysfunction, it may not be the sole determinant. Enlargement of RVEDV increases wall stress by the Laplace relation and augments myocardial oxygen demand, resulting in RV ischemia. Myocardial depressant factors could also be present [16]. Depressed RV contractility may require a marked increase in end-diastolic volume to minimally increase ventricular stroke work and ejected volumes. Significant RV dysfunction in shock, sepsis, and thermal injury has been documented [1–3]. In one study [1] there was no significant correlation between abnormal RV afterload and depressed RVEF. In another study [2], although RV dysfunction was associated with pulmonary hypertension and elevated PVR, the degree of dysfunction was disproportionately large, suggesting a role for other factors.

In our study, the increase in pulmonary pressure in the postoperative period was modest and PVR was not elevated from baseline. This suggests that a change in

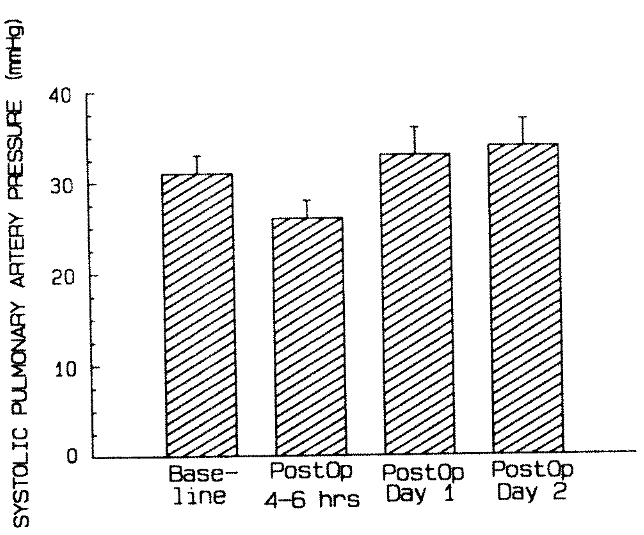

Fig 1. Systolic pulmonary artery pressure significantly increased on postoperative days 1 and 2 above the early postoperative value (p < 0.05), but values were not different from baseline.

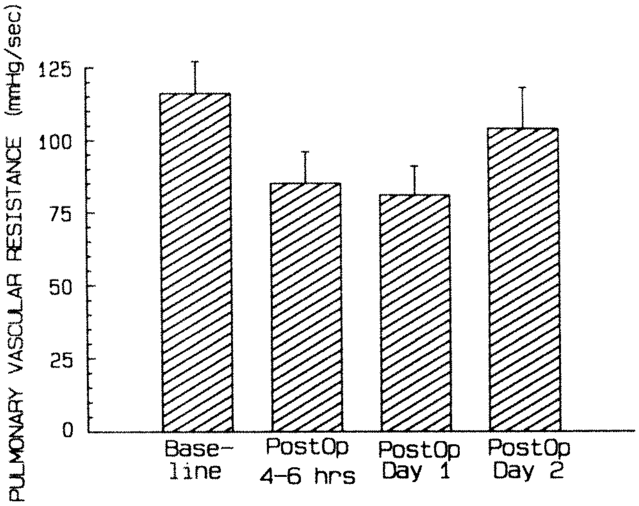

Fig 2. Derived pulmonary vascular resistance was significantly below baseline early postoperatively and on postoperative day 1 (p < 0.05). The value on postoperative day 2 was significantly higher than the early postoperative value.

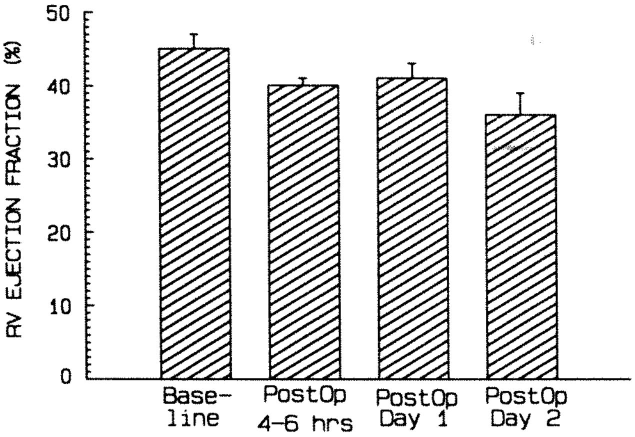

Fig 3. Right ventricular (RV) ejection fraction was significantly decreased from baseline early postoperatively and on postoperative day 2 ($p < 0.05$).

afterload is not the only determinant of the RV dysfunction we observed. The RV dysfunction may be multifactorial, and a contractile deficit may be a factor. We are now studying the possible effect of this factor on RV performance in the postoperative period.

Conventional hemodynamic measurements do not adequately reflect RV performance. For example, central venous pressure remained unaltered in the study despite a significant decrease in RVEF and increase in RVEDV. Cardiac output actually increased despite RV dysfunction. After pulmonary resection, total lung compliance would be changed and intrapleural pressure would be more subatmospheric. Transmural pressures are increased by the incremental decrease in intrapleural pressure. Because the same or lower central venous pressure and PAP may actually represent higher transpulmonary and transatrial pressures, an increase in preload or afterload may be underestimated. However in the present study, intrapleural pressure was held constant during the postoperative study period.

Twenty percent of our patients had development of atrial arrhythmias in the postoperative period. Supraventricular arrhythmias are especially common after pneumonectomy. The etiology has never clearly been documented. This study may support the concept that RV distention is a contributory mechanism. Future studies examining the relationship between RV dilatation and atrial arrhythmogenesis would be appropriate.

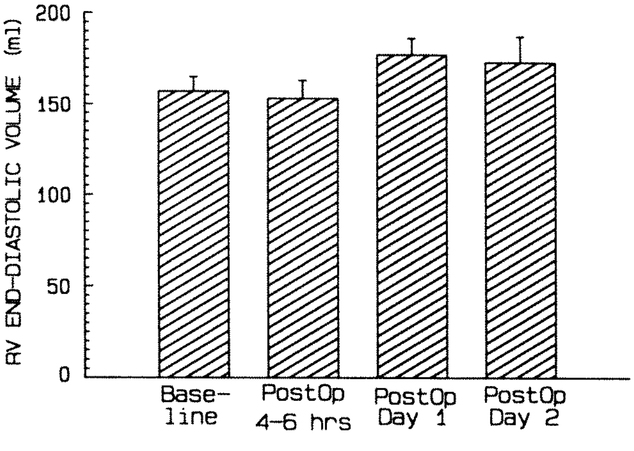

Fig 4. Right ventricular (RV) end-diastolic volume was significantly increased on postoperative days 1 and 2 compared with the early postoperative value ($p < 0.05$).

In summary, serial measurements of RV performance after pulmonary resection identified significant RV dilatation and dysfunction in the early postoperative period. Early detection of a deterioration in RV pump function after pulmonary resection may provide the opportunity for interventional therapy. Thermodilution techniques afford the opportunity to study the effects of pharmacological and hemodynamic manipulation on RV performance perioperatively, which may reduce morbidity after pulmonary resection.

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DISCUSSION

DR WILLIAM A. COOK (North Andover, MA): This is a very provocative report. Did you do any concomitant studies of the blood or fluid volume in this early postoperative period when we know that most patients are quite labile in that respect?

DR REED: They were all kept as equal as possible. Obviously we had to keep them hemodynamically stable, but the central venous pressure, at least preload as far as fluid is concerned, did not change.

DR GORDON F. MURRAY (Morgantown, WV): This is a very nice presentation, and certainly the organization and the excellence of your manuscript is reflected in the presentation. I think you appropriately point out that conventional hemodynamics do not accurately reflect changes in right ventricular function with pulmonary resection. A historical note, which many of the group will recall, as early as 1936 Gibbon and Churchill pointed out that you need to obstruct at least 60% of the pulmonary vascular bed before you get any change in right ventricular output. So you are particularly to be commended for introducing sophisticated thermodilution studies to look at this poorly defined area.

I know you will be interested to know that in 1985 our group in Chapel Hill in Benson Wilcox's laboratory completed a chronic 5-year study of the hypoxic response of beagles after pneumonectomy, and we discovered at that time that the hyperdynamic response of the young animals was more related to the characteristics of the right ventricular function than it was to changes in the pulmonary vascular bed. So I think the direction of your investigation is right on target, and this will probably be the first of several related reports.

I have just two questions. I was interested in the lack of change intraoperatively with the procedures and I wonder if data are available on mean right ventricular pressure or right ventricular end-diastolic pressure, which does increase in a linear or stepwise fashion to pulmonary vascular occlusion. Second, do you plan a longitudinal study to look at these patients later—it is a nice patient population that you have developed—perhaps with stress loading?

DR REED: Thank you, Dr Murray. The answer is no to your first question. We did not have the ability to do that without moving the catheter several times, and we decided this first time to rigidly maintain the catheter where it was.

The answer to your second question is that we are very interested in a long-term study with this group of patients. What I did not mention was that 20% of this population had development of atrial arrhythmias, and those were the patients who had rather severe increases in right ventricular end-diastolic volume. We are in the process now of developing, if you will, each patient's own function curve to first study changes in contractility. Once we get that done, then we will introduce some long-term studies. But we think we need to go back to the benches, as it were, first, and look at contractility.

DR JOSEPH I. MILLER, JR (Atlanta, GA): Did you differentiate between your lobectomy group and your pneumonectomy group? I would make one comment and then ask you to answer that. We have looked at end-diastolic volume, particularly in its implications with postpneumonectomy pulmonary edema, which is the greatest mortality in our pneumonectomy group, and have found distinct differences. When we keep the right ventricular end-diastolic volume low, there is a significant decrease in the incidence of postpneumonectomy pulmonary edema. We found no relation between end-diastolic volume and arrhythmias at all, but wondered, have you differentiated in it by that, because I think the real implications of your study are in the pneumonectomy group.

DR REED: As you know, we only have a small number of pneumonectomies in the series. Because of the presence of the catheter, only left pneumonectomies can be studied. So far we have found no difference between the lobectomies and pneumonectomies. In fact, some of our largest increases in end-diastolic volume have been in the lobectomy group. But we agree with you that it may have more therapeutic implications in the pneumonectomy group. And I think the question about arrhythmias needs to be studied with a larger group of patients to see if this has anything to do with arrhythmias.

DR THOMAS M. EGAN (Chapel Hill, NC): Did you look at any indices of left ventricular function? Could your results be reflecting altered left ventricular function and septal problems?

DR REED: We did not look at anything other than routine measurements, such as mean arterial pressure and cardiac output. In fact, left ventricular function was always better than right ventricular function when we looked at it.

DR JOE B. PUTNAM (Houston, TX): Have you used this catheter in any patients in whom pneumonia or adult respiratory distress syndrome subsequently developed, and if so, were there any hemodynamic changes that were identified?

DR REED: The problem is that right now this study has to be done in the intensive care unit, so this study only goes to postoperative day 1 or 2. In the preliminary group that we studied, one patient in whom severe pneumonia or a condition similar to adult respiratory distress syndrome developed and who was brought back to the intensive care unit. We chose to put the right ventricular catheter in and were astounded at the right ventricular dysfunction that we found. That patient subsequently died.

DR COOK: In developing your further studies, as we intend to hear you back at this podium in the future, let me suggest that many of these patients have a degree of pulmonary disease such that the effects of ventilation therapy and bronchodilator agents would be good to know.

DR REED: Of course one of our goals is to try to introduce some therapeutic manipulations.

Reduced-Size Porcine Lung Transplantation: Long-Term Studies of Pulmonary Vascular Resistance

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The use of isolated adult lobes for pediatric lung transplantation has recently been reported and could potentially help alleviate the profound pediatric donor lung shortage. However, the effect of chronic denervation on pulmonary vasculature of isolated *mature* lobar transplants is not well understood. Previously, we reported that chronic denervation of the *immature* porcine lobe results in abnormal pulmonary vascular compliance. We now present studies of long-term pulmonary hemodynamics in young pigs 12 weeks after transplantation of a reduced-size *mature* left lower lobe. Resting pulmonary vascular resistance of the transplanted mature lobes was similar to that of innervated lobes of age-matched controls. In addition, pulmonary vascular resistance of the transplanted mature lobes did not rise abnormally in response to increased flow caused by clamping the contralateral pulmonary artery. We conclude that denervation of the mature porcine lobe does not result in abnormal pulmonary vascular resistance. In addition, vascular compliance of reduced-size mature porcine lobar transplants is superior to that of denervated reimplanted immature lobes. These findings suggest a deleterious effect of denervation on pulmonary vascular development of the growing porcine lung.

(Ann Thorac Surg 1992;53:583–9)

The introduction of cyclosporine in 1983 for the maintenance of chronic immunosuppression [1] and improvements in bronchial anastomotic techniques [2] together ushered in a new era of successful lung transplantation. As a result, unilateral single-lung transplantation has become an accepted and increasingly reliable treatment option for a number of end-stage pulmonary diseases. For adults, accepted indications for this life-saving procedure continue to broaden as long-term survival improves [3]. In the neonatal and pediatric population, however, a relative donor shortage caused by frequent recipient to donor size disparity has prevented any large series documenting long-term survival after single-lung transplantation. An alternative to the use of pediatric cadaveric lung allografts is the use of reduced-size lung transplants in which a lobe or segment of an adult lung, either cadaveric or living-related, is sculpted to fit the recipient's chest [4]. Although reduced-size lung transplantation has now been reported experimentally as well as clinically [4, 5], long-term functional capacity of these transplants has not been reported.

Experimental lung transplantation with its associated hilar denervation has been well investigated and is known to result in physiologic abnormalities in airway mechanics and pulmonary vascular function [6–9]. Previously, we reported that chronic denervation of the reimplanted *immature* porcine left lower lobe results in abnormal pulmonary vascular compliance when studied after a period of substantial somatic growth. Increasing blood flow through the denervated lobe caused by clamping of the contralateral pulmonary artery resulted in an abnormal rise in pulmonary vascular resistance [10]. Because human postnatal lung development is not complete until early in the second decade [11], transplanting a lung from such a young donor requires denervation before functional and morphologic maturity and may result in similar pulmonary vascular dysfunction.

To investigate the importance of complete lung maturity at the time of transplantation and its possible role in determining functional outcome, we studied pulmonary vascular physiology and gas exchange of reduced-size mature left lower lobe transplants in growing pigs.

Material and Methods

Animal Model and Animal Care

The domestic swine was chosen because of its rapid postnatal lung development [11–13] and because of our familiarity with its tolerance of thoracotomy and lung transplantation. All experimental protocols were reviewed and approved by an institutional animal use committee. The guidelines used by this committee conform to the "Principles of Laboratory Animal Care" put forth by the National Society of Medical Research and the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

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Three animal groups were defined. The first was a control group of 5- to 7-month-old mature pigs with normally innervated left lower lobes. The experimental group consisted of 8- to 10-week-old piglets who were recipients of a reduced-size mature left lower lobe allograft from 6-month-old donors. (At 6 months, most features of porcine lung development are at adult levels [11].) The last group of animals consisted of young piglets who underwent left pneumonectomy with reimplantation of a denervated left lower lobe autograft at 8 to 10 weeks of age. This final group of reimplanted animals served essentially as an additional control group for comparison with the reduced-size transplant group. Some data gathered from this group have previously been reported [10]. All transplant and reimplant procedures in all animals were performed by the same surgeons using the same surgical technique and method of preservation (ice-cold saline flush without prostaglandin infusion) and similar ischemic times. All animals were obtained from a single supplier, and all recipient animals were of similar initial body weight (20 ± 2 kg).

Donor Operation

Mature left lower lobes used for transplantation were explanted from 6- to 7-month-old sexually mature pigs (n = 10) whose mean body weight was 109 ± 5 kg. After induction of anesthesia with intramuscular ketamine (10 mg/kg), the animals were orally intubated and maintained on 1.5% to 2% halothane. The pigs were mechanically ventilated with a volume ventilator (Harvard Apparatus) at a tidal volume of 15 mL/kg and a respiratory rate of 12 to 16 per minute. A left lateral thoracotomy was performed after a subperiosteal resection of the fifth rib. The hemiazygos vein was ligated and divided to gain access to the left main pulmonary artery and superior lobe vein. Both structures were dissected free and isolated, as was the left main bronchus. The left lower lobe vein was then dissected free and the inferior pulmonary ligament sharply divided. The incomplete fissure between the upper and lower lobes was sharply divided, with care to preserve lower lobe parenchyma. The animal was anticoagulated with sodium heparin (100 U/kg intravenously) and the left lung was excised with adequate lengths of artery and vein.

The lung was then immersed in ice-cold physiologic saline slush at 0°C and perfused with heparinized ice-cold normal saline solution through the pulmonary artery at low pressure until the venous effluent returned clear. The upper lobe arteries were then ligated and divided, and the left main bronchus was transected immediately distal to the upper lobe bronchus. Wet weights of the isolated lobes were obtained, and the upper lobe was used for measurements of extravascular lung water and calculation of dry lung weight of the transplanted lobe at time of implantation [14]. The donor animal was then killed with a lethal dose of pentobarbital.

Recipient Operation

At approximately 9 weeks of age, a total of 10 immature piglets (weight 20 ± 2 kg) were designated as transplant recipients of the mature left lower lobes. Beginning 2 days before the transplant procedure all recipient animals received one aspirin (325 mg/day orally) to decrease the risk of pulmonary vein thrombosis. Animals were anesthetized as described in the donor operation and placed on a volume ventilator and maintained on 0.8% halothane. After the intravenous administration of ampicillin (250 mg) and chloramphenicol (500 mg), the recipient pigs underwent a standard left lateral thoracotomy through the fifth intercostal space. A left pneumonectomy was performed after systemic heparinization with sodium heparin (100 U/kg intravenously). The left pulmonary artery was clamped at its takeoff from the main pulmonary artery, the upper lobe veins were ligated, and the lower lobe vein was clamped at its junction with the pyramidal lobe vein and left atrium. The main bronchus was clamped as proximally as possible, and the left lung was excised.

The donor lobe was positioned in the chest and the lower lobe vein was anastomosed first with a running 7-0 absorbable monofilament suture (Maxon; Davis & Geck, Danbury, CT). To compensate for the size mismatch, the recipient vein was opened at its first branch point and this area was used for the anastomosis. The donor lower lobe bronchus was then anastomosed to the recipient lower lobe bronchus by telescoping the recipient main bronchus inside the donor lower lobe bronchus approximately 7 mm. A running 4-0 Maxon suture was used for the back wall of the bronchial anastomosis, and a series of interrupted figure-of-8 sutures was used for the front wall. The bronchus was not wrapped with omentum. The bronchial clamp was released, the tidal volume was adjusted, and the anastomosis was examined for air leaks. Finally, the pulmonary artery was anastomosed using a running 6-0 Maxon suture. Again, any size mismatch was compensated for by opening the recipient vessel through a side branch.

Before the arterial suture was tied, the venous clamp was removed to allow for back-bleeding and deairing. At this time the recipient animal received 500 mg of intravenous methylprednisolone, 1 mg/kg of intravenous azathioprine, and a second 100 U/kg dose of heparin. The arterial suture was then tied and the clamp removed. The vascular anastomoses were examined, and the chest was closed in layers after placement of a chest tube for drainage. The chest tube was removed after 24 hours.

An additional group of 8- to 10-week-old piglets (n = 6) underwent a left pneumonectomy with reimplantation of the native left lower lobe only, after perfusion of the isolated lobe with heparinized ice-cold normal saline solution as described above. This group served as a set of animals whose left lower lobes were denervated at an *immature* stage of development. All transplant and reimplant animals were allowed free access to food and water for the 12-week holding period.

To serve as control innervated left lower lobes, 7 additional pigs aged 5 to 6 months (mean body weight, 109 ± 6 kg) underwent left upper lobectomy acutely at the time of final study, followed immediately by measurements of isolated left lower lobe pulmonary hemodynamics (described below). Four of these 7 study animals survived the entire experimental procedure and represent the control group. These animals were then sacrificed with a pentobarbital overdose.

Immunosuppression

On the day before the transplant procedure, recipient animals received cyclosporine ($18\ \mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{day}^{-1}$ orally; Sandoz Pharmaceutical Corp, East Hanover, NJ), which was continued on a daily basis postoperatively. In addition, recipient animals received methylprednisolone (500 mg intravenously) at the time of transplantation and daily thereafter for 5 days, and azathioprine, 1 mg/kg intravenously at the time of transplantation and 1 mg/kg orally daily thereafter.

Acute rejection was diagnosed when tachypnea, fever, lethargy, and dry cough occurred. These episodes were treated empirically with pulsed methylprednisolone (500 mg intramuscularly) for 3 days. Cyclosporine levels and chest roentgenograms were obtained within the first 2 weeks postoperatively and on a monthly basis thereafter.

In Vivo Studies of Pulmonary Vasculature

Approximately 12 weeks after the transplant procedure, all animals were again anesthetized with ketamine and orally intubated, and a chest roentgenogram was performed to document normal aeration. Of the 10 original recipients of a reduced-size mature lobe, 3 pigs showed little to no aeration of their transplanted lobe and were excluded from further study. At autopsy these pigs were believed to have thrombosed their grafted lobe secondary to pulmonary vein thrombosis. Of the remaining 7 pigs, 1 animal died of cardiac arrest during the terminal study period and 1 animal had an atelectatic, consolidated segment of the transplanted left lower lobe, and complete data from these animals were not available. The remaining 5 animals make up the mature lobar transplant group. Of the 6 animals that received a reimplanted autograft left lower lobe, 5 survived the entire terminal experimental procedure and make up the reimplanted immature lobe group.

Animals were maintained with intermittent intravenous pentobarbital and mechanically ventilated (12 to 15 mL/kg, 10 to 12 breaths/min, inspired oxygen fraction of 1.0). Carotid artery and pulmonary artery catheters were then placed through right common carotid and external jugular venous cutdowns. Carotid artery, central venous, and pulmonary artery pressures were measured continuously with a multichannel recorder (ES1000; Gould Inc, Cleveland, OH). A median sternotomy was performed, and the pulmonary artery catheter was confirmed to be in the main pulmonary artery by palpation. Total pulmonary hemodynamic and systemic hemodynamic measurements were obtained in the resting steady state at end-expiration. Total pulmonary blood flow was measured in triplicate by thermodilution technique using a thermistor-tipped Swan-Ganz catheter.

To verify our blood flow measurements, an attempt was made to dissect free the right and left main pulmonary arteries for placement of ultrasonic flow probes. However, due to dense scar tissue around the previously dissected pulmonary artery, safe placement of the flow probes could not be accomplished in all animals. (In 2 transplant and 2 control animals studied in this manner, flow measured by ultrasonic probes correlated to within 7% of the thermodilution cardiac output. Thereafter, to prevent loss of animals, only thermodilution cardiac outputs were used.) After the pulmonary artery catheter was manually guided into the left main pulmonary artery, resting (before clamping of the right hilum) left lower lobe pulmonary hemodynamic measurements were taken, and the left lower lobe pulmonary vascular resistance was calculated using the entire cardiac output as determined by thermodilution. To increase the cardiac output to the transplanted lobe, the contralateral right pulmonary artery was then totally occluded with an atraumatic vascular clamp and the animals were allowed to stabilize for 10 minutes. Pulmonary hemodynamic measurements of the isolated left lower lobe were then repeated with the contralateral pulmonary artery clamped and *all flow* directed to the left lower lobe, and systemic arterial blood samples were obtained for blood gas analysis. Animals were sacrificed with a lethal dose of pentobarbital after completion of the hemodynamic measurements.

Studies of Gas Exchange

All animals underwent systemic arterial blood gas analysis (inspired oxygen fraction of 1.0) during the period of right pulmonary artery occlusion, with the entire cardiac output shunted through the left lower lobe. In addition, animals that received mature left lower lobe transplants underwent blood gas analysis of right (to serve as control) and left lower lobe pulmonary vein blood samples while breathing room air as a more accurate measure of the reduced-size lobar transplant's ability to oxygenate and ventilate.

Statistics

Measurements are reported as the mean ± standard error of the mean. Student's *t* statistic was calculated for unpaired samples to compare differences between experimental transplant and control groups and for paired samples within the same group when such samples were obtained. A probability value less than or equal to 0.05 was taken to indicate a significant difference between measurements. Comparison of baseline hemodynamics, isolated left lower lobe pulmonary hemodynamic measurements, and blood gas analyses between control innervated left lower lobes, mature lobar transplants, and the denervated reimplanted immature lobes was done by analysis of variance, with a probability value less than or equal to 0.05 indicating significance.

Results

Technical

The mean ischemic time for the transplanted and reimplanted lobes was 167 ± 12 minutes. At the time of transplantation, the mature lobes were significantly larger

Table 1. Resting Hemodynamic Variables[a]

Group	Heart Rate (beats/min)	Aortic Pressure (mm Hg)	CVP (mm Hg)	Main PAP (mm Hg)	Total PVR ($mm\ Hg \cdot L^{-1} \cdot min^{-1}$)
Control LLL (innervated) (n = 7)	101 ± 4	115 ± 5	9 ± 1	29 ± 1	1.8 ± 0.1
Mature LLL transplants (n = 6)	123 ± 3	87 ± 6[b]	9 ± 1	25 ± 1	1.4 ± 0.1
Reimplanted immature LLL (n = 6)	130 ± 14[b]	122 ± 6[c]	9 ± 1	24 ± 3	2.6 ± 0.4[b,c]

[a] Data are mean ± standard error of the mean. [b] $p \leq 0.05$ versus control LLL. [c] $p \leq 0.05$ versus mature LLL transplants.

CVP = central venous pressure; LLL = left lower lobe; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance.

than the entire immature left lungs that they replaced, as determined by wet weight (141 ± 10 versus 66 ± 6 g; $p \leq 0.05$). Extravascular lung water fractional content was the same between the mature lobes and immature lungs (0.92 ± 0.01).

At time of final study, all animals (controls, mature lobar transplants, and reimplanted immature lobes) were of similar postnatal age (20 to 22 weeks) and weight (83 ± 3 kg). We saw no bronchoscopic evidence of bronchial anastomotic strictures in any of the animals that received a transplanted or reimplanted left lower lobe. In addition, postmortem studies revealed no evidence of pulmonary vascular anastomotic strictures in any of the animals with a viable left lower lobe allograft or autograft.

Pulmonary Hemodynamics

Resting baseline systemic hemodynamic variables of all animal groups are presented in Table 1. Baseline total pulmonary vascular resistance was similar between the control innervated lobes and mature lobar transplants. However, the total pulmonary vascular resistance of the animals whose left lower lobes were reimplanted at a young age was significantly higher ($p \leq 0.05$).

Isolated left lower lobe pulmonary hemodynamic measurements of innervated controls, reduced-size mature lobar transplants, and reimplanted immature lobes are shown in Table 2. The values are expressed as mean ± standard error of the mean before and after occlusion of the right pulmonary hilum. No significant hemodynamic differences were seen between the transplanted mature lobes and normally innervated lobes either before or after occlusion of the contralateral pulmonary artery. Most importantly, clamping of the contralateral pulmonary artery did not cause an abnormal rise in the pulmonary artery pressure or pulmonary vascular resistance of the transplanted mature lobes.

However, when comparison was made with the animals who had undergone denervation of their left lower lobe before complete pulmonary development, significant differences in cardiac output and subsequent pulmonary vascular resistance were seen ($p \leq 0.05$). Most importantly, clamping the contralateral pulmonary artery resulted in an abnormal rise in pulmonary vascular resistance in the lobes denervated at a young age ($p \leq 0.05$). Although mean pulmonary artery pressure rose more than in the innervated control or mature transplanted lobes, this was not significant.

Table 3 represents the observed increase in pulmonary vascular resistance in all three groups that occurred after clamping of the right pulmonary artery. Again, the transplanted mature lobes demonstrated a change very similar to the control innervated lobes, indicating a normal ability to maintain cardiac output and vasodilate in response to the increased lobar flow. However, the lobes that were

Table 2. Isolated Left Lower Lobe Pulmonary Hemodynamics[a]

	PAP (mm Hg)		PCWP (mm Hg)		CO (L/min)		PVR ($mm\ Hg \cdot L^{-1} \cdot min^{-1}$)	
Group	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control LLL (innervated) (n = 4)	27 ± 2	46 ± 3	13 ± 1	18 ± 1	9.0 ± 0.8	7.7 ± 1.4	1.6 ± 0.2	4.0 ± 0.6
Mature LLL transplants (n = 5)	31 ± 2	49 ± 2	13 ± 1	17 ± 2	9.2 ± 0.9	6.5 ± 0.8	2.1 ± 0.4	5.4 ± 0.9
Reimplanted immature LLL (n = 5)	25 ± 3	60 ± 13	12 ± 1	20 ± 3	5.5 ± 0.4[b,c]	3.7 ± 0.7[b,c]	2.6 ± 0.3[b]	12.9 ± 3.9[b,c]

[a] Data are mean ± standard error of the mean. [b] $p \leq 0.05$ versus control LLL. [c] $p \leq 0.05$ versus mature LLL transplants.

CO = cardiac output; LLL = left lower lobe; PAP = pulmonary artery pressure; PCWP = pulmonary capillary artery pressure; Post = after clamping of the contralateral pulmonary artery; Pre = before clamping of the contralateral pulmonary artery; PVR = pulmonary vascular resistance.

denervated and reimplanted at an immature age demonstrated a rise in pulmonary vascular resistance that was significantly higher than the other two groups ($p \leq 0.05$).

Blood Gas Analysis

Systemic blood gas analysis with the entire cardiac output shunted through the left lower lobe (after clamping) of all three groups is presented in Table 4. No significant differences were seen in oxygen tension, carbon dioxide tension, or pH between the three groups, indicating adequate long-term gas exchange in the reduced-size lobar transplant. Before termination of the experiment, animals in the mature lobar transplant group were changed to room air ventilation for 15 minutes and blood samples were obtained from the right and left pulmonary veins to further analyze the ability of the transplanted mature lobe to oxygenate and ventilate. These results are presented in Table 5. Again, no significant differences were seen between the transplanted mature lobe and the normally innervated right lung.

Comment

Transplantation of an isolated pulmonary lobe or segment from a more mature donor into an immature recipient is technically feasible. Although this type of transplant has been reported both experimentally and clinically [4, 5], long-term functional studies of such reduced-size transplants have not been reported. In Crombleholme and associates' [4] recent report of reduced-size lung transplantation in neonatal swine, short-term studies of the pulmonary vasculature demonstrated no increase in pulmonary artery pressure and only a slight increase in pulmonary vascular resistance in the more mature lobe immediately after transplantation. Crombleholme and associates suggested that the more mature lobar graft was better able to accommodate the blood flow from the neonatal recipient, despite denervation. These studies in the early posttransplantation period yielded results similar to our own; however, Crombleholme and associates' studies were only in the resting state. The response of the transplanted reduced-size lobe to an acute rise in blood flow and its ability to modulate pulmonary vascular resistance chronically were not studied. In clinical single-lung or lobar transplantation, the contralateral lung will always be abnormal. Thus, studies in experimental models in which there is flow through a normal contralateral lung are insufficient. Studies of vascular compliance under conditions of high flow are necessary before reduced-size transplants can be widely offered as a reliable long-term treatment option for children with end-stage pulmonary disease and to help determine whether mature lobes or immature lungs should be used for donor organs.

Most previous studies of pulmonary hemodynamics after experimental lung or lobar reimplantation or allotransplantation have been performed in adult animals with fully developed lungs. The issue of abnormal pulmonary hemodynamics remains unsettled. Many authors note an abnormally high or fixed pulmonary vascular resistance in transplanted or reimplanted lungs, perhaps due to an inability of the denervated lung to vasodilate appropriately [8–10, 15–17]. However, other authors have noted completely normal pulmonary vascular resistance after experimental lung transplantation and claim most problems with abnormal pulmonary vascular resistance are caused by an improperly constructed pulmonary venous anastomosis [18, 19]. We use absorbable suture material for all bronchial and vascular anastomoses to avoid the complication of fixed strictures and to allow for growth of the anastomoses.

Table 3. Changes in Pulmonary Artery Pressure and Pulmonary Vascular Resistance Caused by Clamping of the Contralateral Pulmonary Artery[a]

Group	Change in PAP	Change in PVR
Control LLL (innervated) (n = 4)	18.5 ± 3.6	2.4 ± 0.4
Mature LLL transplants (n = 5)	17.6 ± 2.1	3.2 ± 0.5
Reimplanted immature LLL (n = 5)	34.8 ± 10.3[b]	10.3 ± 3.6[c,d]

[a] Data are mean ± standard error of the mean. [b] $p \leq 0.09$ versus mature LLL transplants. [c] $p \leq 0.05$ versus control LLL. [d] $p \leq 0.05$ versus mature LLL transplants.

LLL = left lower lobe; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance.

Table 4. Systemic Arterial Blood Gas Analysis With Entire Cardiac Output Shunted Through the Left Lower Lobe (After Clamping)[a]

Group	pH	$PaCO_2$ (mm Hg)	PaO_2 (mm Hg)[b]
Control LLL (innervated) (n = 4)	7.39 ± 0.04	42 ± 6	202 ± 69
Mature LLL transplants (n = 5)	7.34 ± 0.04	47 ± 6	179 ± 37
Reimplanted immature LLL (n = 4)	7.40 ± 0.04	48 ± 6	126 ± 46

[a] Data are mean ± standard error of the mean. [b] Inspired oxygen fraction = 1.0.

LLL = left lower lobe; $PaCO_2$ = partial pressure of carbon dioxide in systemic arterial blood sample; PaO_2 = partial pressure of oxygen in systemic arterial blood sample.

Table 5. Pulmonary Venous Blood Gas Analysis of Reduced-Size Lobar Transplants While Breathing Room Air[a]

Lung	$PvCO_2$	PvO_2
Native right lung	31 ± 4	108 ± 11
Mature LLL transplant	32 ± 4	77 ± 11[b]

[a] Data are mean ± standard error of the mean. [b] No significant difference by paired t test versus native right lung.

LLL = left lower lobe; $PvCO_2$ = partial pressure of carbon dioxide in pulmonary venous blood sample; PvO_2 = partial pressure of oxygen in pulmonary venous blood sample.

The pulmonary vascular physiology of experimentally transplanted or reimplanted *immature* lungs has only recently been studied and reported. We reported that reimplantation of the left lower lobe in young piglets results in decreased vascular compliance of that lobe when studied chronically [10]. The present results show that denervation of the *mature* porcine lung does *not* result in long-term abnormal pulmonary vascular physiology. We believe that the functional differences that exist after denervation of the immature as compared with the mature lung are related to the degree of pulmonary maturation at the time of denervation.

The degree to which normal lung development is dependent on intact neural stimulation and the effects of denervation on subsequent development and function of an immature lung are not completely understood. Our present results support the hypothesis that denervation before complete maturation of the immature porcine lung has a profound effect on subsequent function. Because the pulmonary vascular functional abnormalities seen in denervated immature lobes are not present in transplanted mature lobes, we believe that intact neural input is required for proper pulmonary vascular development of the porcine lung and interruption of this pathway results in long-term vascular dysfunction. Correlation between porcine and human lung development [11] would suggest that clinical transplantation of an organ younger than 10 to 12 years may result in similar vascular dysfunction.

Although neural regeneration of a transplanted lung may occur [20], denervation during a critical period of lung development may be enough to produce profound long-term functional abnormalities. In the normally innervated, healthy pulmonary vascular bed, an increase in flow results in capillary recruitment with a resultant decrease in pulmonary vascular resistance and maintenance of pulmonary artery pressure [21]. Denervation of the immature pulmonary vasculature seems to impair this normal physiologic response, whereas denervation of the mature pulmonary vasculature does not. It is possible that capillary recruitment was facilitated in the mature lobe due to its larger size at the time of transplantation. However, because airway physiology of the denervated immature porcine lung is also abnormal [6], we believe that denervation of the immature porcine lung impairs subsequent development of that lung and that the manifestations of this denervation include profound long-term functional abnormalities. Further experimental studies and clinical correlation to human lung transplant recipients will be critical. Our data suggest that transplantation of mature lung tissue may be functionally superior to immature allografts when the need for pediatric lung transplantation arises.

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DISCUSSION

DR THOMAS M. EGAN (Chapel Hill, NC): I think this is an exciting approach to a difficult problem, the problem of a very critical shortage of pulmonary donors. I have a couple of questions. Although your pulmonary arterial anastomoses are open at autopsy, did you measure any pressure difference across them? I ask because they still represent a fixed diameter, and when you divert the entire cardiac output, one of the ways that the pulmonary artery compensates is to increase its diameter.

The second question is, with respect to comparing a mature lobe transplanted as a single lung to an immature lobe, would it not be more appropriate to have compared that with an intact lung in terms of pulmonary vascular resistance? Were you disappointed that your pulmonary vascular resistance in these immature lobes that functioned as lungs appeared to be elevated?

DR KERN: With respect to the first question, all of the vascular anastomoses were done with absorbable suture to avoid fixed stenoses. Nevertheless, the way we measured pulmonary vascular hemodynamics was with the sternum open so we could manually guide the pulmonary artery catheter into the pulmonary artery to be studied. Pressure measurements were made proximal and distal to the anastomoses, and there were no pressure gradients detectable.

We agree that chronic studies in an experimental model of single whole lung transplantation are needed, especially to study the effects of chronic denervation on pulmonary growth. We initially began this project to study the effects of denervation on pulmonary vascular and airway physiology after transplantation. Therefore, we did not want to complicate the matter by using a whole lung, which in this animal model is often complicated by superior lobe vein thrombosis. We have since developed a technique of single whole lung transplantation in this immature porcine model, using for the superior lobe vein anastomosis an atrial cuff on the donor vein going into the left atrial appendage of the recipient. We will shortly begin airway and vascular studies and studies of lung growth in these chronic animals.

Finally, although we were surprised to find abnormal pulmonary vascular responses in the denervated immature lobes, we believe the finding of normal hemodynamics in the mature lobes suggests that proper innervation is required for normal pulmonary vascular development of the porcine lung.

Isolated Lung Transplantation for End-Stage Lung Disease: A Viable Therapy

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Since January 1990, we have performed 29 isolated lung transplantations in 28 patients with end-stage lung disease (12 single, 16 bilateral). Recipient diagnoses were: cystic fibrosis (11), chronic obstructive pulmonary disease (6), pulmonary fibrosis (6), eosinophilic granulomatosis (1), postinfectious lung disease (1), adult respiratory distress syndrome (1), and primary pulmonary hypertension (2). There have been four deaths, two in patients with pulmonary fibrosis and two in patients with primary pulmonary hypertension. Four patients have undergone transplantation while on ventilatory support for respiratory failure (2 with cystic fibrosis, 1 having redo lung transplantation with cystic fibrosis, and 1 with adult respiratory distress syndrome); all of these have survived. Six patients required cardiopulmonary bypass, which was associated with increased transfusion requirement. All patients 2 months after discharge have returned to an active life-style, except for 2 patients who currently await retransplantation. Preoperative pulmonary rehabilitation has resulted in significant improvement in exercise performance in all patients. Immunosuppression consists of cyclosporine, azathioprine, and antilymphoblast globulin (University of Minnesota), withholding systemic steroids in the early postoperative period. We have employed bronchial omentopexy in all but four transplants; there has been one partial bronchial dehiscence, two instances of bronchomalacia requiring internal stenting, and one airway stenosis. Cytomegalovirus disease has been seen frequently (15 cases), but has responded well to treatment with ganciclovir. Other complications have included one drug-related prolonged postoperative ventilation, thrombosis of a left lung after bilateral lung transplantation requiring retransplantation, five episodes of unilateral phrenic nerve palsy after bilateral lung transplantation (4 resolved), and the requirement of massive transfusion (>10 units) in 5 patients. Isolated lung transplantation can be performed with acceptable morbidity and mortality in properly selected patients with a variety of end-stage lung diseases.

(Ann Thorac Surg 1992;53:590–6)

In the last decade, unprecedented development has occurred in the field of pulmonary transplantation. Since the first successful heart-lung transplantation in 1981 [1] and the first successful isolated lung transplantation in 1983 [2], pulmonary transplantation has become a therapeutic modality that has been applied to a variety of causes of end-stage lung disease. More than 600 isolated pulmonary transplants have been reported to the Washington University Lung Transplant Registry (Joel D. Cooper; personal communication). Recently, Washington University reported excellent results of a program that was initiated in 1988. Sixty-six patients underwent 69 transplant procedures with an operative crude survival of 83% and an actuarial 1-year survival of 79%. Excluding the first eight double-lung transplantations performed using a tracheal anastomosis, the 1-year actuarial survival was 86% [3].

This article reports the experience of a different center with a program that was modeled on the University of Toronto and Washington University lung transplant programs. The favorable result reported by the Washington University Lung Transplant Group can be achieved at other centers. There remains a distressing shortage of suitable pulmonary organ donors to enable application of this exciting therapy to larger numbers of patients.

Patients and Methods

In the last 2 years, we have seen more than 130 patients with a variety of end-stage lung diseases for consideration of pulmonary transplant. Since January 1990, 28 patients have undergone 29 isolated lung transplant procedures (12 single, 16 double, and 1 redo double-lung transplantation). Our program currently has 26 patients listed awaiting lung transplantation. Nine patients have died awaiting transplantation, and 5 other referred patients have died before completion of evaluation and formal listing.

Of the 28 patients who underwent transplantation, 15 were male and 13 were female. The mean age was 33.4 years (range, 16 to 63 years). The distribution of diagnoses

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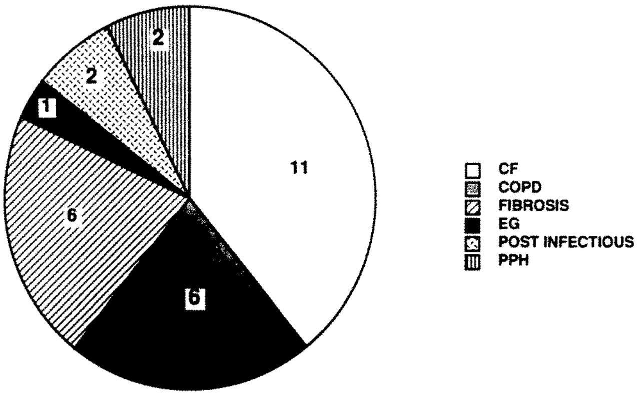

Fig 1. Distribution of diagnoses of patients undergoing lung transplantation. More than one third of the patients in our series had cystic fibrosis. (CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; EG = eosinophilic granulomatosis; PPH = primary pulmonary hypertension.)

of these patients is depicted in Figure 1. The preponderance of recipients with cystic fibrosis (11 patients) reflects the presence of an active cystic fibrosis center at this institution. Recipients with pulmonary fibrosis included 1 patient with radiation/bleomycin-induced pulmonary fibrosis for successful therapy of Hodgkin's disease 6 years before transplantation. One patient had end-stage lung disease attributed to allergic bronchopulmonary aspergillosis. A second case of "postinfectious" end-stage lung disease was that of a 20-year-old man with adult respiratory distress syndrome secondary to *Legionella* pneumonia. He had been ventilated for more than 4 months before receiving his bilateral lung transplant. This patient was one of 4 patients successfully undergoing transplantation during an interval of ventilatory support [4]. A 32-year-old man with cystic fibrosis required retransplantation 7 days after double-lung transplantation for graft failure. At explantation, the left transplanted lung had undergone venous thombosis and the right transplanted lung had evidence of severe adult respiratory distress syndrome. Two other patients with cystic fibrosis had development of acute respiratory failure while waiting for suitable donor organs, required mechanical ventilation, and could not be weaned. They underwent transplantation after 9 and 12 days of mechanical ventilatory support, respectively.

Double-lung transplantation was performed in all 11 patients with cystic fibrosis, as well as the 2 patients with postinfectious end-stage lung disease. Two patients with chronic obstructive pulmonary disease had double-lung transplantation. One had concomitant bronchiectasis and 1 underwent double-lung transplantation because of his young age (28 years). One patient with pulmonary hypertension had double-lung transplantation because the second lung could not be placed in North America on the day of transplantation. All 6 patients with fibrotic lung disease and the 1 patient with eosinophilic granulomatosis underwent single-lung transplantation, as did 4 patients with chronic obstructive pulmonary disease and 1 with primary pulmonary hypertension.

Patient Selection

The criteria that we have employed to select appropriate recipients are similar to those used by other programs [5]:

End-stage lung disease with evidence of progression of disease and life expectancy <18 to 24 months
No other systemic disease
No major coronary artery disease
Ability to move to transplant center and participate in preoperative rehabilitation program, and maintain self plus support person for 3 to 6 months
Demonstrated compliance with medical regimens
No contraindication to immunosuppression
Psychological stability; no history of alcohol or drug abuse or psychosis
Mobility: must be ambulatory with O_2 as required
Not on systemic steroids
For single-lung transplantation, age <60 years with no chronic infectious lung disease (eg, chronic bronchitis, bronchiectasis, cystic fibrosis)
For double-lung transplantation, age <50 years

We have decreased our acceptable age limit for recipients from 65 to 60 years, as more younger patients were seen and evaluated for transplantation and increasing numbers of patients died waiting for transplants. It also became clear that transplantation was a major stress that was less well tolerated by older patients. We are increasingly circumspect of recipients over the age of 50 years because of these concerns.

A program of preoperative and postoperative pulmonary rehabilitation in the form of monitored, graded, aerobic exercise (treadmill, lower extremity ergometry) is an important component of our program for patients with end-stage respiratory disease. Those patients with pulmonary hypertension awaiting lung transplantation do not participate in this program, but in general, these patients are frequently less debilitated than those with end-stage parenchymal lung disease.

Operative Techniques

Techniques employed for single-lung transplantation have been described elsewhere in detail [6]. These are performed through a standard posterolateral thoracotomy. Preoperative perfusion scan identifies the least perfused lung, and this is generally the side selected for isolated single-lung transplantation. All double-lung transplantations have been performed using the bilateral technique described by Pasque and associates [7]. The "worst" lung is removed first, followed by implantation of the allograft on that side. We have used omentopexy routinely because of concerns related to bronchial anastomotic healing, except for 4 consecutive patients (patients 17 to 20) in whom airway anastomoses were performed according to the method described by Trinkle's group [8]. We abandoned this technique because of an increased incidence of airway anastomotic complications and have returned to routine omentopexy (unpublished results).

Pulmonary retrieval is performed in the setting of multiple organ retrieval. We prefer to remove the heart

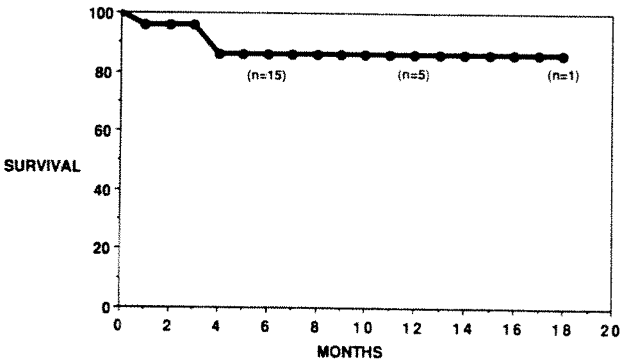

Fig 2. Actuarial survival after isolated lung transplantation (single or double).

first, then excise the double-lung block, with esophagus and thoracic aorta included [9]. These are removed on the back table, and the lung block is divided into separate right and left lungs for implantation. Before harvest, the lungs are flushed with Euro-Collins solution (80 to 100 mL/kg) modified by the addition of $MgSO_4$ (8 mEq/L) and glucose.

Immunosuppression

Our regimen of immunosuppression is modeled on the early methods employed by the University of Toronto and Washington University [9] and consists of cyclosporine, azathioprine (Imuran; Burroughs Wellcome Co, Research Triangle Park, NC), and University of Minnesota antilymphoblast globulin for the first 2 weeks, attempting to avoid steroids for the first 2 to 3 weeks postoperatively. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy is performed 1 week and 3 weeks after transplantation and every 3 months for the first year. In addition, bronchoscopy is performed to investigate a new infiltrate, unexplained fever, or decreased oxygen saturation or exercise tolerance.

Results

Twenty-four of the 28 patients are current survivors, for a crude survival rate of 86%. The actuarial survival at 6 months and 12 months is 82.7% (Fig 2). Follow-up is short for our series, with the longest surviving patient now at 18 months after operaton.

The average wait for a transplant in our series has been 82 days (range, 7 to 216 days) but is clearly becoming longer, and many of our currently listed patients have been waiting 6 months or longer. Hospital stay has varied from 16 days to in excess of 5 months, but has averaged 5 weeks for all survivors.

In general, early lung function has been excellent in most recipients despite an average ischemic time of 332 minutes (range, 92 to 525 minutes). Hypothermic modified Euro-Collins flush appears to be an acceptable method of pulmonary preservation for ischemic times up to almost 9 hours.

Mortality

Four deaths have occurred in the series to date. A 32-year-old woman with idiopathic pulmonary fibrosis underwent left single-lung transplantation and subsequently had development of *Staphylococcus aureus* pneumonia. Despite appropriate antibiotic therapy, she continued to have respiratory failure requiring prolonged ventilatory support. The patient and her family refused retransplantation, and she ultimately died of *Candida* sepsis from a cavity in the transplanted lung.

A 63-year-old man, the oldest patient in our series, had right single-lung transplantaton for idiopathic pulmonary fibrosis. On the second postoperative day he self-extubated and aspirated. This resulted in serious hemodynamic compromise and respiratory failure. He died of sepsis 10 days postoperatively.

A 39-year-old man with severe primary pulmonary hypertension had right single-lung transplantation. Severe pulmonary edema developed in the early postoperative period, and he died of refractory hypoxemia the first posttransplant day.

A 38-year-old man underwent double-lung transplantation for primary pulmonary hypertension. He had substantial problems with airway necrosis and bronchomalacia requiring placement of bronchial endoluminal stents in both transplanted lungs. His convalescence was hampered by multiple pulmonary emboli and development of respiratory failure. He died of multiple organ failure 5 months after transplantation.

Morbidity

Six patients have required prolonged ventilation (>7 days). Three of these have been described above. A recipient of a double-lung transplant for chronic obstructive pulmonary disease had development of haloperidol-induced Parkinson's disease requiring prolonged ventilation, which resolved with discontinuance of the drug. The 32-year-old man who underwent retransplantation 7 days after his first operation had development of renal failure requiring dialysis and was ventilator dependent for 21 days, but ultimately was weaned and recovered. The young man who underwent transplantation because of adult respiratory distress syndrome required ventilation for 27 days after transplantation because of severe respiratory muscle weakness and bronchomalacia. He was subsequently discharged ventilator independent and without the need for supplemental oxygen.

Five instances of unilateral phrenic nerve palsy after double-lung transplantation have occurred in our series. One of five phrenic nerve palsies persists. We attribute this complication to the use of metal retractors in the vicinity of the phrenic nerves to facilitate exposure of the hilar structures during double-lung transplantation. Since abandoning the use of metal retractors and using only hands for retraction, we have not seen this complication.

Five patients have required transfusion of greater than ten units of packed red cells intraoperatively. All were recipients of double-lung transplants. Three of these were patients who required cardiopulmonary bypass because of an inability to tolerate one-lung anesthesia. Two patients with postinfectious lung disease had severe pleural scarring resulting in considerable blood loss with mobilization of their native lungs. The other 3 patients, 2 of whom required cardiopulmonary bypass, had cystic fibrosis.

Infection has been a source of mortality and morbidity. All patients are treated perioperatively with prophylactic antibiotics. In patients with infective end-stage lung disease, antibiotic selection is tailored to the most recent preoperative respiratory cultures. In patients with cystic fibrosis, *Pseudomonas* tracheobronchitis has been observed but has not been difficult to treat. Cytomegalovirus (CMV) disease (defined as the demonstration of CMV in tissue) has been seen frequently in our recipients (15 cases) and has not been confined to CMV-positive recipients. Our series includes two instances of CMV pneumonia in CMV-negative recipients of CMV-negative grafts. Nevertheless, this pathogen has been responsive to ganciclovir therapy.

An unusual problem was observed in a 44-year-old man who underwent single-lung transplantation for chronic obstructive pulmonary disease. Postoperatively, bullae from the native lung herniated across the midline, resulting in serious atelectasis of the transplanted lung. The transplanted organ could be adequately ventilated only with double-lumen tube ventilation, and when this was discontinued, atelectasis occurred again, necessitating a bullectomy of the native lung to gain ventilator independence. This patient went on to be discharged from the hospital and achieved a good functional result before fever and a pulmonary infiltrate in the transplanted lung developed. Open lung biopsy demonstrated caseating granulomata, and cultures grew *Mycobacterium tuberculosis*. Despite antituberculous therapy, the transplanted organ has been severely damaged, and this patient is awaiting retransplantation.

A 32-year-old man with idiopathic pulmonary fibrosis underwent single-lung transplantation at a time of serious exacerbation of his illness. His postoperative course was stormy, marked by recurrent episodes of bronchospasm necessitating reintubation and reinstitution of mechanical ventilatory support. Pathologic examination of the explanted lung demonstrated idiopathic pulmonary fibrosis and, in addition, an acute bronchiolitis (Fig 3A). Although no viral pathogen was identified, in retrospect it was recalled that other members of the patient's family were ill at the time with a respiratory infection, and we assume that the acute bronchiolitis was viral in nature and had an effect on the implanted lung. This patient recovered and had an acceptable level of function, but his condition deteriorated several months after transplantation, leading to an open lung biopsy 6 months after transplantation that documented obliterative bronchiolitis (Fig 3B). He is currently awaiting retransplantation.

One patient required revision of her pulmonary artery anastomosis for substantial narrowing resulting in an inordinate blood flow to the native emphysematous lung after transplantation. The patient with pulmonary hypertension who underwent transplantation had multiple pulmonary emboli documented 2 weeks after transplantation. This patient also had an embolic cerebral hemisphere event, presumably related to paradoxic emboli across a patent foramen ovale. One other cerebrovascular accident occurred in the series, in the patient who underwent redo double-lung transplantation, presumably embolic from thrombus in the left atrium at the time of explantation of the thrombosed left lung. This patient recovered fully.

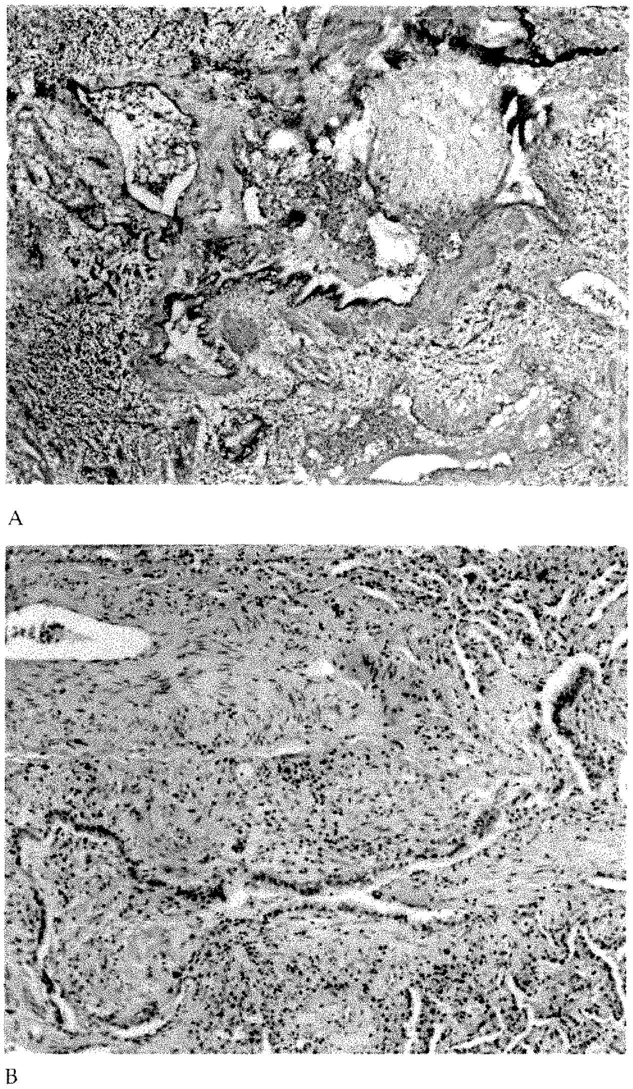

Fig 3. (A) Acute bronchiolitis superimposed on idiopathic pulmonary fibrosis in a recipient of a single-lung transplant. (B) Open lung biopsy specimen 6 months after transplantation shows obliterative bronchiolitis.

Preoperative and postoperative pulmonary function data are depicted in Figures 4 and 5, excluding the 2 patients with primary pulmonary hypertension and 1 patient with adult respiratory distress syndrome for whom no premorbid pulmonary function test results were available. Recipients of single-lung transplants (see Fig 4) have demonstrated improvement in forced vital capacity and forced expiratory volume in 1 second in the range of 50% predicted. Recipients of double-lung transplants have, as expected, demonstrated better improvement in spirometry (see Fig 5). This has not corresponded to a difference in functional result as assessed by improved performance in the 6-minute walk (Fig 6).

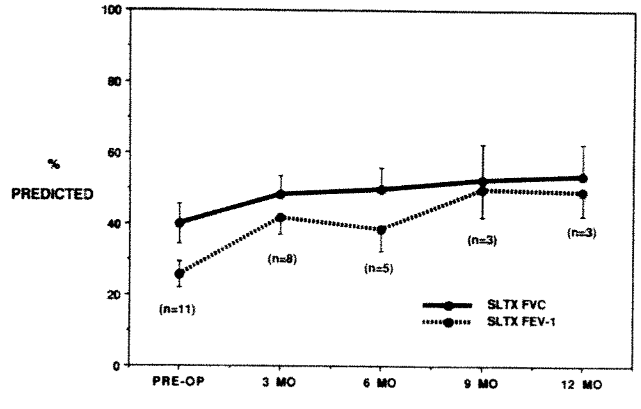

Fig 4. Forced vital capacity (FVC) *and forced expiratory volume in 1 second* (FEV_1) *(% predicted, mean ± standard error of the mean) for recipients of single-lung transplant* (SLTX), *excluding 1 patient with primary pulmonary hypertension.*

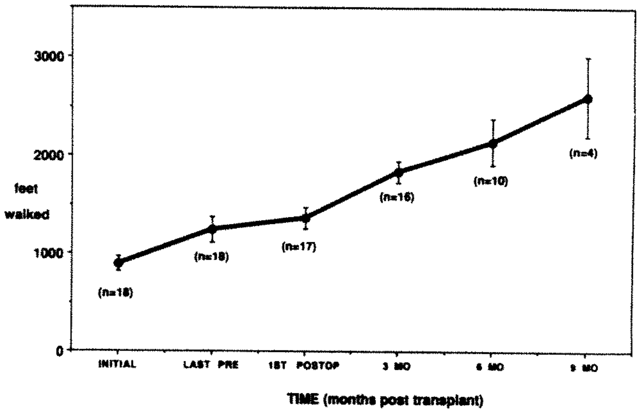

Fig 6. Results of 6-minute walk test (mean ± standard error of the mean) in recipients of isolated lung transplant. Only 18 patients with any postoperative data are included. One patient's first postoperative 6-minute walk was at 3 months because of a stroke, which resolved.

Aside from the 2 patients awaiting retransplantation, all recipients who have been discharged from the hospital have returned to an active life-style off oxygen and have been restored to health.

Comment

Patients with end-stage lung disease represent a formidable challenge. Lung transplantation is a logistic endeavor comprising many components. Proper patient selection, physical rehabilitation, careful postoperative monitoring, and posttransplantation physical therapy are all vital components to a successful outcome that vie with attention to operative detail in predicting a successful outcome. Although this group of patients is a challenge, we have found it very rewarding to restore chronically ill patients to health, particularly those in a young age group.

We have been particularly fortunate in our experience with patients suffering from cystic fibrosis. Other groups have championed heart-lung transplantation for this disorder. Yacoub and colleagues [10] reported a 78% actuarial 1-year survival in 27 patients undergoing heart-lung transplantation for cystic fibrosis. The group from Papworth [11] has reported a similar 72% survival rate at one year in 32 patients with cystic fibrosis who underwent heart-lung transplantation. Heart-lung transplantation, however, mandates cardiopulmonary bypass with inherent bleeding complications. Additionally, the organ distribution mechanism in the United States prioritizes cardiac grafts; hence, few heart-lung grafts are available for transplantation. This makes isolated lung transplantation a more attractive alternative, and we are very pleased with our early results, particularly in patients with cystic fibrosis.

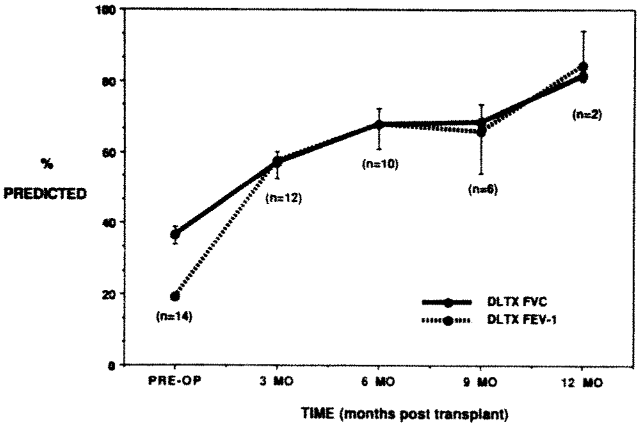

Fig 5. Forced vital capacity (FVC) *and forced expiratory volume in 1 second* (FEV_1) *(% predicted, mean ± standard error of the mean) for recipients of double-lung transplant* (DLTX), *excluding 1 patient with primary pulmonary hypertension and 1 (preop) patient with adult respiratory distress syndrome.*

To date, isolated lung transplantation for primary pulmonary hypertension at our institution is disappointing. Both patients in our series with this diagnosis died, 1 early after transplantation of florid pulmonary edema, and 1 after a prolonged hospital course complicated by ischemic airway problems and multiple pulmonary emboli. Levine and associates [12] described success in 2 of 3 patients who underwent single-lung transplantation for primary pulmonary hypertension, and the Washington University Group [3] has had excellent results with 6 patients with primary pulmonary hypertension and 2 with Eisenmenger's syndrome associated with an atrial septal defect. All 8 patients survived to the time of reporting. Trinkle has cautioned that patients with primary pulmonary hypertension in whom bronchiolitis obliterans subsequently develops after single-lung transplantation quickly establish a severe ventilation perfusion mismatch, because the bulk of perfusion continues to go to the poorly ventilated transplanted lung if small airway disease intervenes (J. Kent Trinkle; personal communication). Although there is no doubt that patients with pulmonary hypertension can be palliated with single-lung transplantation, it remains to be seen whether this is the most efficient use of a scarce resource.

Last year, 262 patients received isolated lung transplantation in the United States [13]. Currently, 551 patients are listed for isolated lung transplantation and another 165 patients for heart-lung transplantation [14]. Despite the increasing numbers of lung transplantations being performed, waiting lists are growing longer each month, attesting to the critical shortage of suitable pulmonary donors. A recent study has estimated that as many as 25% of current cardiac donors in the United States may have lungs that are suitable for transplantation [15]. Even if all of these potential donors were realized, the supply would still fall far short of the demand. This obliges transplant programs to diligently select patients who are ill enough to justify the risks of transplantation while maximizing the opportunity for survival to minimize organ wastage.

What is a reasonable estimate of survival? According to the Washington University Lung Transplant Registry, actuarial survival for lung transplant recipients increased from 50% for transplantations performed before 1989 to 69% for transplantations performed in 1989 or later. There was a modest survival advantage to single-lung transplants, according to the Registry (65.9% actuarial 1-year survival for all single-lung transplants reported, compared with 62.8% actuarial 1-year survival for bilateral lung transplants and 58.2% actuarial 1-year survival for double-lung transplants) (Joel D. Cooper; personal communication). This Registry had accounted for 637 isolated lung transplants up to April 1991 but, because it is voluntary, may overestimate the actual survival.

By adhering to previously published principles of appropriate patient selection, and by taking a programmatic approach to isolated lung transplantation, we have been able to achieve a 1-year actuarial survival of 82%. This includes some patients who admittedly were at higher risk because of ventilator dependency. An urgent need exists to increase the size of the current pulmonary donor pool. This will allow more widespread application of this exciting therapy to larger numbers of patients with end-stage lung disease.

The long-term results of lung transplantation are unclear. Some patients will succumb to opportunistic infections, lymphoproliferative disorders, or bronchiolitis obliterans. However, the majority of patients who survive the operation to be discharged from the hospital will enjoy a substantial improvement in the quality of life and, likely, the quantity of life.

We express our appreciation to Betsy Mann for her editorial expertise in the preparation of the manuscript, and to Dr R. Reddick for providing the photomicrographs.

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DISCUSSION

DR J. ALEX HALLER, JR (Baltimore, MD): Dr Egan, I was very interested in that particular group of patients who had cystic fibrosis, and I will direct my questions to that group. One of the fascinating things to me about your experience is that these patients do not seem to have difficulty from their systemic disease. We have good ways of managing patients with cystic fibrosis for their pancreatic insufficiency and for their intestinal abnormalities, such as meconium ileus, but the lung has been the big problem, and I would like to ask you what your experience so far has been. I realize this is a relatively short follow-up, but perhaps you can give us perspective on the literature for the long-term follow-up on these patients.

As the pulmonary tissue is replaced in these patients, does it continue to have reasonable function? What about tracheal cilial abnormalities, which are a part of the systemic disease of cystic fibrosis? What is your feeling about the long-term impact of the systemic disease on your single organ transplant?

DR EGAN: In our hands, the group of patients with cystic fibrosis has been a very gratifying group in whom to perform transplantation. Although we have been concerned with the degree of pulmonary contamination, we have been very pleased with our results, and the postoperative infectious complications have been, to date at least, relatively straightforward and easy to deal with.

In terms of our long-term survival, all of our 11 patients depicted here have been discharged from the hospital, are off oxygen, and are fully ambulatory. Our longest survivor with cystic fibrosis is now 13 months out. He has normal pulmonary function tests and is currently looking for employment.

The tracheal abnormalities that you allude to, although present histologically, do not appear to have a major functional component. Other groups with longer follow-up, either in heart-lung or lung transplantation for these patients, have very gratifying results, and indeed the Stanford group has suggested that patients with cystic fibrosis may have a reduced risk of bronchiolitis obliterans developing in the allograft. And so this is a very gratifying group of young patients in whom to perform transplantation.

DR WILLIAM A. BAUMGARTNER (Baltimore, MD): This is a very nice series of patients in the tradition of the Washington group. I wonder if you might expand on the evolving indications for single-lung transplantation, specifically addressing those patients with primary pulmonary hypertension. In your series both patients with primary pulmonary hypertension died, and I think it is now becoming evident around the country that this is a group of patients in whom perhaps single-lung transplantation may not be an effective form of therapy.

DR EGAN: We have had serious morbidity in patients with pulmonary hypertension. One of our recipients received a bilateral lung transplant and one received a single-lung transplant. The patient who received the bilateral lung transplant died of causes unrelated to his pulmonary hypertension, we believe. There is no question that these patients are more difficult to manage postoperatively. Nevertheless, the experience from other centers would indicate that single-lung transplantation for this disorder is possible, and that although the morbidity is higher than that for other groups, one can achieve a satisfactory survival, at least in the short-term. The group from San Antonio, as you know, has raised the specter of these patients getting into serious problems when bronchiolitis obliterans develops because of the substantial amount of ventilation-perfusion mismatch that occurs in a setting of one lung receiving all the perfusion. So I think for this disease the jury is still out as to whether or not single or bilateral lung transplantation is the appropriate procedure.

DR FREDERICK L. GROVER (Denver, CO): I enjoyed your report very much. I would like to reiterate my concern regarding patients with pulmonary hypertension. This has been the group with the highest morbidity and mortality in the San Antonio series, and I think the final answer as to which procedure is best for this group is unknown. I am curious about your problems with the bronchial anastomosis without an omental wrap. We got into that somewhat accidentally in San Antonio because our first patient did not have omentum and healed nicely, and then after that we did not use omentum and actually have had no major problems. I hope I can do as well in Denver with it.

I am interested in how you did your anastomosis. We use nonabsorbable 4-0 Prolene. The principles are not to clean the bronchus at all and to leave as much tissue on it as possible, to keep the donor bronchus as short as possible, with perhaps just one ring before the take-off of the upper lobe so as to minimize the problems with blood supply. Could you amplify on your techniques?

DR EGAN: We have performed our anastomoses in an end-to-end fashion except in the 4 patients who did not have omentopexy, and we attempted to use the techniques described so well by Dr Trinkle in San Antonio, which involve essentially telescoping the bronchus one ring with an end-to-end approach on the membranous portion. We have not had the same gratifying results that Dr Trinkle has had with that approach, although we have avoided perioperative steroids.

The suture that we use is a polyglycolic acid suture, Maxon, running on the membranous wall and interrupted Vicryl sutures on the cartilaginous wall. We do make an effort to make this an end-to-end anastomosis, and we do make an effort to have a minimal amount of donor airway, usually one ring or at most two rings, from the upper lobe take-off.

Diagnosis and Management of Congenital Vascular Rings: A 22-Year Experience

Karen Chun, MD, Paul M. Colombani, MD, David L. Dudgeon, MD, and J. Alex Haller, Jr, MD

Division of Pediatric Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Between 1968 and 1990, we operatively treated 39 patients (19 boys, 20 girls) with congenital aortic arch anomalies. Median age was 7 months (range, 1.5 months to 23 years). Thirty-seven patients (95%) had respiratory symptoms. Barium swallow was diagnostic in 95%. Right arch with aberrant left subclavian artery and double aortic arch were the most common types (11 each). Treatment of an aortic diverticulum was documented in 19 patients; the aortic diverticulum was excised (9), managed by aortopexy (7), or left in situ (3). Postoperative recovery was rapid, with a median intensive care unit stay of 2 days, time to oral feeding of 1 day, and postoperative time to discharge of 7 days. Two deaths occurred: 1 infant had undergone emergent operation for control of hemorrhage from an aortotracheal fistula due to tracheostomy tube erosion, and the other had multiple associated congenital heart defects. Postoperative complications included bleeding (1), pneumonia (5), and chylothorax (1). One boy had persistent severe symptoms due to an untreated aortic diverticulum and underwent subsequent excision of the aortic diverticulum with complete relief of symptoms. Median length of follow-up was 12.5 months, with at least 97% of survivors completely or nearly completely free of symptoms from the vascular ring. These results suggest that early repair of congenital aortic vascular rings, including fixating or excising an associated serious aortic diverticulum, is safe and effective and allows for normal tracheal growth.

(Ann Thorac Surg 1992;53:597–603)

Vascular rings and other congenital aortic arch anomalies may be a major cause of tracheoesophageal obstruction in neonates. Division of the ring has become the standard of surgical treatment; operative management of an associated aortic (Kommerell's) diverticulum, however, is much less clearly defined. Since 1968 we have operatively managed 39 cases of symptomatic aortic arch anomalies, including 19 aortic diverticula. We undertook this study to assess general outcome, including improvement in airway function, with a particular focus on treatment of an associated aortic diverticulum.

Clinical Materials and Results

Between January 1968 and December 1990, 39 cases of congenital vascular rings were surgically treated at the Johns Hopkins Children's Medical and Surgical Center on the Pediatric Surgery service. Patients with associated congenital heart anomalies, for which open heart surgical correction was simultaneously undertaken, were excluded from the retrospective study except for 1 boy whose vascular ring was repaired *before* definitive treatment of concomitant congenital heart defects.

Aortic arch anomalies were categorized according to the Mayo Clinic classification [1]. In this series, the most common types were double aortic arch (Mayo type IA, 11 or 28%) (Fig 1) and right aortic arch with aberrant left subclavian artery (Mayo type IIIB1, 11 or 28%) (Fig 2). Of the double arch rings, the right posterior arch was dominant in 7 (64%). Seven patients (18%) had double arch with atretic left arch (IB); 4 (10%) had right arch with mirror-image branching (IIIA); 3 (8%) had isolated anomalous innominate arteries; and 2 (5%) had isolated aberrant right subclavian arteries that arose from a left descending thoracic aorta and coursed behind the esophagus. The presence or absence of an associated aortic diverticulum was documented by angiography or at operation in 29 patients (74%).

Median age at presentation was 7 months (range, 6 weeks to 23 years). Eighty percent of the patients were less than 2 years of age when first seen, and 64% were less than 1 year of age. There were 19 boys (49%) and 20 girls (51%).

Thirty-seven patients (95%) had respiratory symptoms, which consisted of stridor, cough, wheezing, or a combination of these symptoms. Thirteen (35%) of these patients also had dysphagia or evidence of poor feeding. Only 2 patients had dysphagia alone. One of these was a 23-year-old woman who had had an incomplete repair of her vascular ring at an outside facility during childhood. The other was a 4-month-old infant with gastroesophageal reflux and failure to thrive. The median duration of symptoms before presentation was 4.5 months; the average duration was 16.3 ± 4.8 months (range, 1 month to 11 years).

Seventeen patients had had from 1 to 4 episodes of

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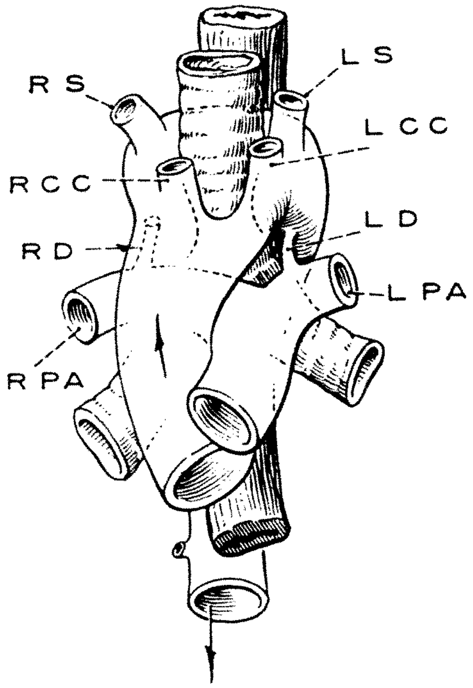

Fig 1. Double aortic arch, Mayo type IA vascular ring. Trachea and esophagus are encircled by the vascular ring. (LCC = left common carotid artery; LD = left ductus; LPA = left pulmonary artery; LS = left subclavian artery; RCC = right common carotid artery; RD = right ductus; RPA = right pulmonary artery; RS = right subclavian artery.)

pneumonia for which they were treated on an outpatient basis or were hospitalized. Often symptoms were noted at birth but diagnosis was delayed because medical attention was not sought or because the underlying condition was not suspected by the primary physician. Most commonly, in these latter cases, symptoms were ascribed to bronchitis, tracheitis, or asthma.

Associated congenital anomalies were present in 6 patients. A vascular ring was not initially suspected in 1 patient with a laryngeal web that was treated by laser multiple times before eventual division of his vascular ring. Another had Rubenstein-Tabyi syndrome with mental retardation. Imperforate anus with perineal fistula were associated anomalies in 1 other patient. The latter also had horseshoe kidney and vesicoureteral reflux. Two additional patients also had vesicoureteral reflux, and 1 of these had pectus carinatum. The only patient with associated congenital heart disease was found, after division of his vascular ring, to have a double-outlet right ventricle and pulmonary stenosis which required an open heart operation.

One patient presented with a major complication of her anomaly. She was initially seen in extremis with exsanguinating hemorrhage from a tracheoaortic fistula resulting from erosion of a previously placed tracheostomy tube into a vascular ring.

A familial incidence occurred only once: 2 sisters were affected with type IIIB1 rings. At the time of repair of the older sister's vascular ring at 8 years of age, her 1-year-old sister was being evaluated for the same condition.

Diagnostic Evaluation

Barium esophagograms were obtained in all patients and were diagnostic in all but 2, both of whom were found to have anomalous innominate arteries. Aortography was performed in 87% with 100% accuracy. Computed tomographic scanning was not performed on any patient; more recently, however, magnetic resonance imaging (MRI) has been used instead of angiography to avoid intravenous contrast medium injection. In this study, MRI was diagnostic for a vascular ring per se in all 3 of the patients for whom it was obtained but was incorrect as to the type of ring in 1 patient. In this patient a double arch was diagnosed by MRI but was found to be a right arch with aberrant left subclavian artery at operation.

Operative Management

Exposure was through a standard left posterolateral thoracotomy incision in 34 cases (87%). Median sternotomy was performed for the 3 cases of anomalous innominate artery and for the emergent case of tracheoaortic fistula. One patient underwent bilateral thoracotomy for repair of a type IA ring with a dominant left arch. In this unusual patient, a left patent ductus arteriosus was first ligated and divided through a left thoracotomy; a right thoracotomy was then required for division of the nondominant right arch and for reimplantation of an aberrant right subclavian artery. In the 7 patients with double arch and dominant right arch, the nondominant left arch was divided either between the left common carotid and left subclavian arteries or just distal to the left subclavian artery. In the case of a nondominant right arch, the arch

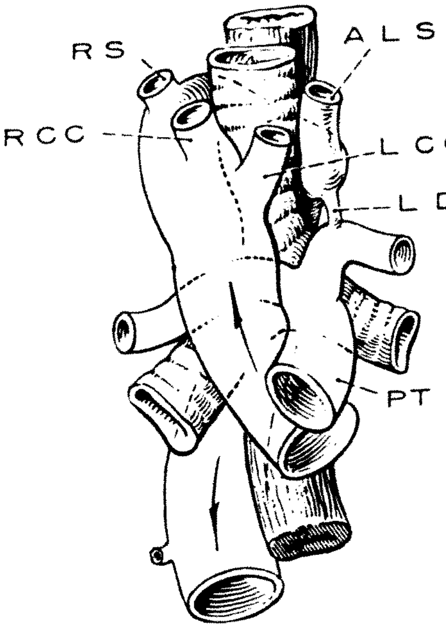

Fig 2. Right aortic arch with aberrent left subclavian artery, Mayo type IIIB1 vascular ring. Left ductus completes the vascular ring formed by the anomalous right aortic arch and aberrent left subclavian artery. (ALS = aberrent left subclavian artery; LCC = left common carotid artery; LD = left ductus; PT = pulmonary trunk; RCC = right common carotid artery; RS = right subclavian artery.)

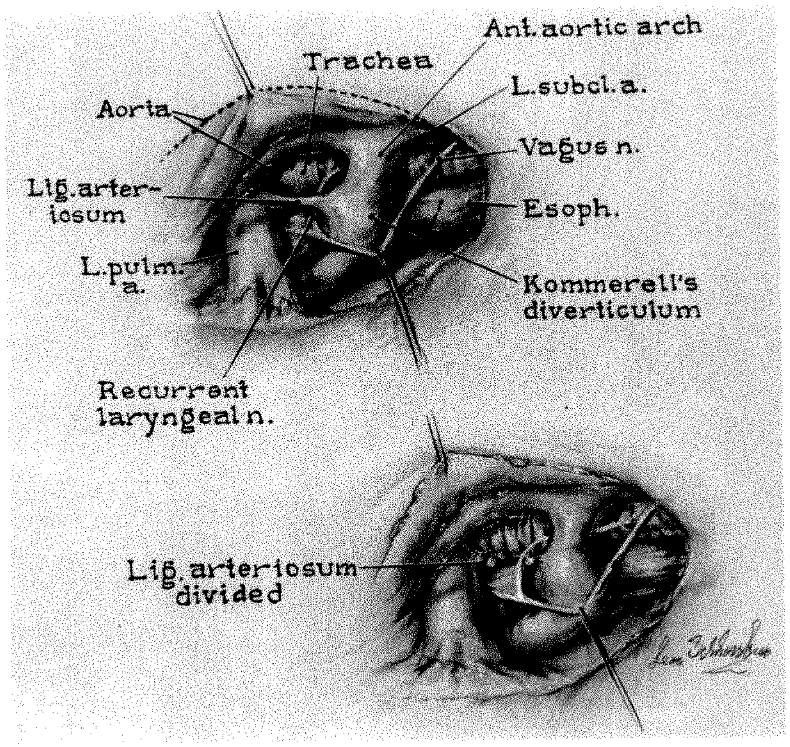

Fig 3. *(Upper) Exposure of Mayo type IA vascular ring through a standard left posterolateral thoracotomy incision. The left anterior aortic arch gives rise to the left subclavian artery just proximal to Kommerell's diverticulum. Trachea and esophagus are compressed within the vascular ring. (Lower) Repair of vascular ring—division of ligamentum arteriosum. Ligamentum arteriosum has been doubly ligated and divided. Kommerell's diverticulum intact.*

was divided between the right common carotid and right subclavian arteries. The ligamentum arteriosum or patent ductus arteriosus was suture ligated and divided in all cases (Figs 3, 4).

Patients with type IIIB1 vascular rings generally underwent division of the left ligamentum arteriosum (Fig 5). In all patients with complete or partial vascular rings, after division of the ring, the esophagus and trachea were extensively freed from the surrounding adventitial tissues.

Treatment of an aortic diverticulum was documented in 19 of 29 cases. The diverticulum was excised flush with the aorta in 9 patients (see Figs 4, 5), managed by aortopexy in 7 (Fig 6), and left in situ in 3. The mode of treatment was determined by the operating surgeon's preference. There was no significant difference in mode of treatment of a diverticulum among the 4 types of vascular rings (IA, IB, IIIA, IIIB).

Anomalous innominate arteries were treated by suspension to the sternum. One isolated aberrant retroesophageal right subclavian artery was managed by division without reimplantation in an 8-month-old boy. No evidence of subclavian steal has been noted.

In the patient for whom emergent operation was required, exsanguinating hemorrhage from tracheostomy tube erosion was found arising from a tracheoaortic fistula just distal to the right subclavian artery in a type IA vascular ring. Division of the right posterior arch at the bleeding site controlled the hemorrhage. The tracheal defect was then repaired with a pericardial patch.

Outcome

Among the 37 survivors, postoperative recovery was rapid with a median intensive care unit stay of 2 days (range, 1 to 46 days), median time to oral feedings of 1 day (range, 1 to 14 days), and median postoperative time to discharge of 7 days (range, 4 to 135 days). None of these patients required tracheostomy or prolonged ventilatory support. No instances of recurrent laryngeal nerve injury were documented. Complications occurred in 13 patients

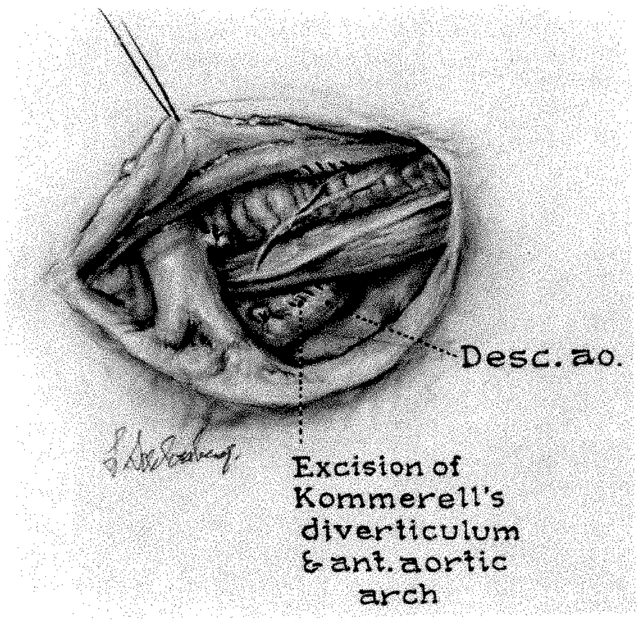

Fig 4. *Excision of Kommerell's diverticulum. Completed repair of Mayo type IA vascular ring. The left anterior arch has been divided just distal to the origin of the left subclavian artery. Left ductus has been doubly ligated and divided. Kommerell's diverticulum has been excised flush with the descending aorta.*

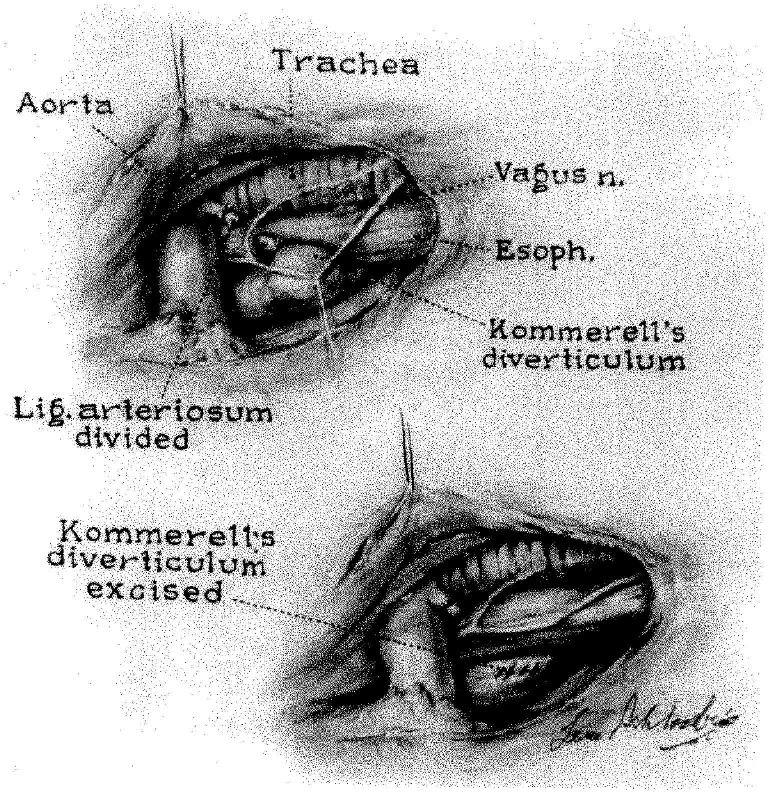

Fig 5. (Upper) Repair of type IIIB1 vascular ring. Left ligamentum has been doubly ligated and divided. Kommerell's diverticulum remains intact. (Lower) Excision of Kommerell's diverticulum. Vascular ring has been divided. Aortic diverticulum has been excised flush with the descending aorta.

(33%) and included postoperative bleeding requiring reoperation for control (3), respiratory arrest with reintubation (2), pneumonia (5), pneumothorax (1), and sepsis (1). Four patients had development of chylothorax, 1 bilaterally. Two of these required operative ligation of the thoracic duct; the others were successfully managed by chest tube drainage and dietary restriction. One boy had persistent severe symptoms due to partial obstruction of the trachea by an untreated aortic diverticulum. He underwent subsequent excision of the diverticulum with

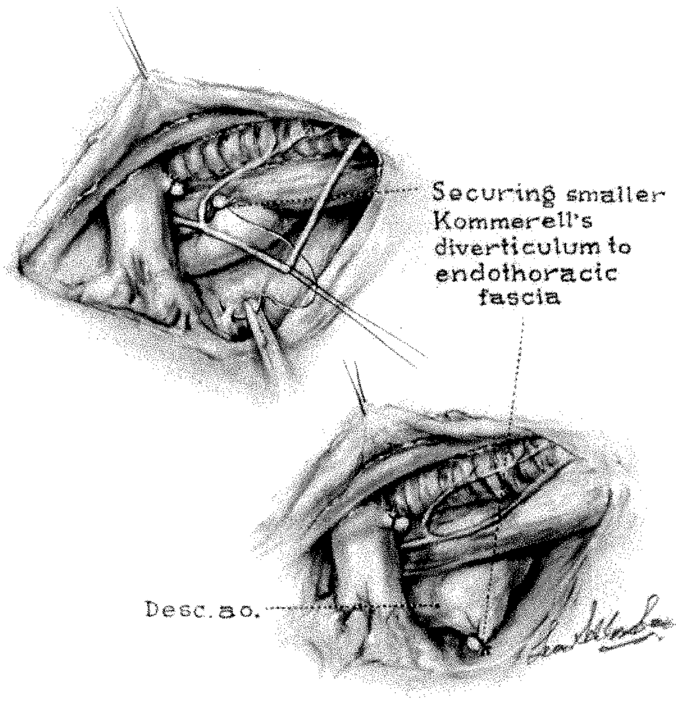
Securing smaller Kommerell's diverticulum to endothoracic fascia
Desc. ao.

Fig 6. Aortopexy of Kommerell's diverticulum. (Upper) Vascular ring has been divided. (Lower) Kommerell's diverticulum is secured to endothoracic fascia (aortopexy), leaving the adjacent trachea and esophagus completely free of extrinsic compression.

complete relief of symptoms. This is the patient who prompted our belief that a large retained diverticulum may cause residual obstruction. Another infant's hospital stay was prolonged by a recurrent congenital laryngeal web that required repetitive laser treatments.

Two deaths occurred (5%); one was in the infant with tracheoaortic fistula. Twenty-four hours after emergent repair of the fistula and division of her vascular ring, the patient was returned to the operating room for control of bleeding from the proximal right arch stump. The patient's condition then deteriorated over the ensuing 20 days. The other death occurred in a 2-month-old boy with double-outlet ventricle and pulmonary stenosis who underwent a routine type IA vascular ring repair. His postoperative course was complicated by apneic/cyanotic spells that forced a decision to proceed with definitive correction of the congenital heart defects. The open heart repair was unsuccessful and the patient eventually succumbed to multiple organ failure.

Median length of follow-up of 32 survivors was 12.5 months (range, 10 weeks to 20 years). Five patients (13%) were lost to follow-up. Of the patients with documented clinic or emergency room visits after discharge, 12 (38%) were asymptomatic and 15 (47%) had mild residual symptoms (cough, brassy voice) at 6 months to 1 year after repair. Respiratory symptoms required no specific treatment and improved gradually over approximately 1 year concomitant with tracheal growth. Less than optimal outcome was related to persistent clinical conditions that were unrelated to vascular ring repair, ie, reactive airway disease, esophageal stricture, recurrent laryngeal web, and gastroesophageal reflux with failure to thrive in 1 patient each. The single patient with a poor operative result was ultimately asymptomatic after reoperation for his aortic diverticulum.

Comment

The safety and effectiveness of immediate operative repair of symptomatic congenital vascular rings has been confirmed by multiple authors [2–6]. Correction in early infancy relieves dyspnea and dysphagia, prevents aspiration-induced pneumonia and other respiratory infections, and most importantly, allows for normal tracheal growth. Since the mid-1970s we have been performing selective excision of an associated Kommerell's aortic diverticulum in addition to division of the ring. Aortopexy of the aortic diverticulum is an alternative to excision in some cases. Clinical evidence suggests that the diverticulum may be a major cause of residual tracheal or esophageal compression and if left in situ after division of the vascular ring, may result in continuing obstructive symptoms [7]. Resection of the diverticulum has also been advised by Campbell [8] because aneurysmal dilation of the diverticulum is known to occur.

In our series 2 patients required reoperation for persistent symptoms after incomplete ring division. One of these patients was the 23-year-old woman who had had a vascular ring operation in childhood and presented with a 4-month history of dysphagia. Despite reoperation with excision of an aortic diverticulum and lysis of adhesions around the esophagus, the patient continued to complain of dysphagia. She was subsequently diagnosed as having an esophageal stricture and spastic esophageal dysmotility. Her case was complicated by concomitant chronic psychiatric difficulties including drug dependency, and thus a functional rather than organic cause may, at least partly, account for the less-than-optimal result. In the case of the other patient who underwent reoperation for an incompletely divided vascular ring, the results were remarkable. The patient was seen at 4 months of age with respiratory symptoms since birth. He underwent division of his type IB ring, but postoperatively continued to have serious respiratory symptoms including apnea requiring reintubation. After reoperation and excision of an associated aortic diverticulum his symptoms disappeared. Thus, although we could not make any valid statistical comparisons relative to diverticulum treatment because of the small number of cases in each group, we believe that aggressive management of the Kommerell diverticulum by aortopexy or excision of the diverticulum is indicated in the surgical management of congenital aortic vascular rings.

Exposure through a left thoracotomy incision is generally accepted as the operation of choice for division of a vascular ring. Jung and associates [7] once recommended a right thoracotomy, but we found that a standard left posterolateral thoracotomy provided excellent exposure in all but 1 case. A right thoracotomy or median sternotomy is, however, the approach of choice for division *and anastomosis* of an isolated anomalous right subclavian artery [5]. An anomalous innominate artery may be approached through a median sternotomy or a right anterolateral thoracotomy to suture the artery to the undersurface of the sternum.

A barium esophagogram is extremely reliable in diagnosing a vascular ring but does not delineate the precise vascular anatomy. Aortography has been the gold standard in providing a preoperative road map of the anomaly [9]. Angiograms may be confusing, however, because of overlapping of various vessels [10] and may not distinguish a IB (one arch atresia) from a IIIB1 anomaly (right arch with aberrant left subclavian). Recently we have been using MRI as a noninvasive alternative to aortography. Diagnostic accuracy was 100% for a vascular ring in 3 patients, but accurate delineation of the vascular anomaly appeared to be less clear than with aortography because vascular ring type was incorrectly interpreted in 1 of the 3 patients. With the rapid evolution of this technology, however, and with more experience interpreting the scans and because it is not invasive, MRI may soon supersede aortography, especially in the pediatric population, as the diagnostic modality of choice in the definitive work-up of patients with congenital vascular rings [11, 12].

Our review reiterates the effectiveness of surgical intervention in infancy or early childhood for congenital vascular rings. For the routine patient with an isolated aortic arch anomaly that is diagnosed in infancy, early surgical repair results in complete or nearly complete cure. Most patients can be discharged between 4 and 7 days postoperatively. A slower regression of respiratory symptoms is expected in some patients because of preexisting pulmonary disease and mild to moderate tracheomalacia. Concomitant major congenital anomalies were the causes of prolonged hospital stay, rehospitalization, poorer outcome, and death.

Clinical suspicion of a vascular ring as the cause of serious tracheoesophageal obstruction in a young child should lead to early diagnosis and referral for operative treatment. Serious airway compromise as well as recurrent respiratory infections and destructive pneumonitis can produce chronic illness and debilitation in older children and adults. Such a course can be prevented by early diagnosis and definitive operative treatment, including aggressive management of an associated Kommerell's diverticulum.

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DISCUSSION

DR CONSTANTINE MAVROUDIS (Chicago, IL): I would like to congratulate Dr Haller on a beautifully presented landmark report and also to share a piece of nostalgic history. J. Willis Potts, whom he knew well, was the first chief of Cardiac Surgery at Children's Memorial Hospital in Chicago. His clinical contribution to the surgery of vascular rings is well documented. This resulted in a large experience which included the first description of successful treatment of a pulmonary artery sling in 1954. Since 1947, surgeons at Children's Memorial Hospital have performed more than 225 operations for vascular rings with a 5% early and 5% late mortality. The mortality was highest in the early years. Over the last 15 years, the mortality has been quite low and relates to preexisting associated cardiac anomalies. The excellent results presented by Dr Haller and his associates mirrors the great traditions of his own and sister institutions. I noticed that the authors did not present their experience with pulmonary artery sling. We have employed pericardial patch tracheoplasty with cardiopulmonary bypass with excellent results. I would like to ask the authors how they manage this difficult group of patients. I enjoyed this report very much.

DR HALLER: I am very pleased that you brought up Dr Potts' name in the discussion, because he was one of the early surgeons managing children with congenital heart abnormalities as well as the vascular rings. The reason we did not include any pulmonary artery slings in this group of patients is because we excluded all patients who required a concomitant open heart operation. Those who required open heart operations and happened to have associated vascular rings, such as an aberrant left pulmonary artery, are not included in this series. In answer to your question, we would manage those pulmonary slings with open heart surgical techniques because of the necessity of dividing the ring within the mediastinum.

DR JOSEPH T. WALLS (Columbia, MO): I enjoyed your report very much. We have just reviewed a 34-year experience with vascular ring; however, there were fewer patients in our series. We also noticed that only a few patients had intracardiac anomalies. One of the important aspects of treatment reinforced in the review was that in addition to any other maneuvers required to divide the vascular ring, one should explore the ductus or ligamentum area to make sure it is also released. One of the patients had a pexing procedure, and I was somewhat skeptical of the technique, but a 17-year follow-up showed that it held up very nicely.

Of other importance in our experience was that 2 people, 1 with an aberrant right subclavian artery arising as the fourth branch off of the arch, had development of an aneurysm later in life—this was not one that was initially treated but was picked up de novo as an aneurysm. Also, one who had a double aortic arch surgically interrupted had an ascending aortic aneurysm and aortic valve insufficiency develop in adulthood which required aortic valve and root replacement. In follow-up, did any of your patients have degenerative disease of the remaining arch vessels?

DR HALLER: Thank you very much for your comments. I am familiar with 1 patient who had an aneurysm develop in the aortic diverticulum, which is another reason for excising it, but only 1 or 2 such patients have been reported. None of our patients has had development of degenerative diseases up to this point in a 22-year follow-up of them. You notice that there were some patients who were lost to follow-up, and that always makes you nervous, but of those we were able to follow, there were no long-term vascular problems associated with dividing the vascular ring.

DR ED L. HOOVER (Buffalo, NY): I too enjoyed the report very much, and I wonder if you ever see problems akin to tracheomalacia or persistent tracheal obstruction, particularly in the children who are operated on at a somewhat older age. If you have, can you predict those children who will need a tracheal resection at the time, or have you had to go back at a later date to repair them secondarily?

DR HALLER: We did not have a chance to emphasize some of the associated tracheomalacia-type symptoms, but they are in our group called "good." All of these children ultimately outgrew airway symptoms, and it was not necessary to carry out any tracheal reconstruction in this group of patients. I believe most of them are on the basis of compression, and the earlier the ring is divided the better likelihood that the trachea will grow and develop and not have long-term sequelae. If you do not operate on them until they are older children or young adults, then you may have persistent problems with tracheomalacia.

DR MICHAEL S. SWEENEY (Houston, TX): The last questioner asked the question that I was going to ask, but I would like to add my congratulations to Dr Haller. I can remember slogging through a few of these with you. As a matter of fact I think I can most easily identify with your talk when you show the "complications" slide. But at any rate, congratulations. It is a truly noteworthy experience from a very creative and very talented surgeon.

DR HALLER: Thank you very much, Dr Sweeney. It is certainly true that the residents take care of most of the complications, am I right, President Sade? Thank you very much.

Effects of Intraaortic Balloon Position on Renal Artery Blood Flow

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Debate continues over what happens to renal blood flow when intraaortic balloons are adjacent to the renal arteries. Fourteen dogs were prepared by implanting instruments to measure heart rate; right atrial, pulmonary arterial, carotid arterial, and femoral arterial pressures; cardiac index; mixed venous oxygen saturation; urine output; and left and right renal blood flows. A 12-mL intraaortic balloon was inserted through the left (n = 9) or right (n = 5) femoral artery. The position of the balloon was randomized so that it was initially placed in either the control (thoracic) or renal position (at the level of the renal arteries). Intraaortic balloon pumping was performed for 4 hours in each position. In 8 dogs, at least one of the renal arteries had partial occlusion, 23% to 98% decrease in flow (mean decrease, 66%), while the intraaortic balloon was in the renal position. An intraaortic balloon in the renal position results in lower renal blood flow as well as a high risk (57%) of selective renal artery occlusion. Decreased renal blood flow is not apparent using conventional monitoring, as hemodynamics do not change.

(Ann Thorac Surg 1992;53:604–10)

Studies have been performed to evaluate the importance of intraaortic balloon (IAB) position. Previous work [1–3] has focused on IABs in the ascending or thoracic aorta and the effects of these positions on cardiac function. Little, if any, laboratory work has been done to evaluate what effect IABs placed in the abdominal aorta have on renal function and blood flow. Clinical studies have documented a variety of complications associated with IABs. The most common complications are limb ischemia with or without thrombus formation, vascular injuries, and infection at the insertion site [4–9]. There are, however, reports [10, 11] describing complications that may be attributed to partial or total occlusion of the renal or mesenteric arteries by the IAB. These complications are sometimes a result of improper balloon placement. This study verifies the importance of correct IAB position in the thoracic aorta and may be useful in the development of future IABs for adults and children.

Material and Methods

Experiments were performed on 14 adult mongrel dogs of both sexes weighing 20 to 25 kg. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 85-23, revised 1985).

Anesthesia was induced with thiamylal sodium, 10 to 15 mL intravenously. The animals were intubated with a cuffed endotracheal tube and then ventilated with 100% oxygen using a pressure/volume ventilator. Anesthesia was maintained with 1% to 2% halothane (Fluothane; Wyeth-Ayerst Laboratories, Philadelphia, PA). Temperature was maintained at 37° ± 1°C. A cutdown was performed on the right side of the neck, and a 7F oximetric thermodilution catheter was inserted into the internal jugular vein and floated into the pulmonary artery. An arterial pressure–monitoring catheter was inserted into the right carotid artery.

A midline abdominal incision was made, and Transonic flow probes (Transonic Systems Inc, Ithaca, NY) were placed around the left and right renal arteries and connected to a Transonic dual-channel flowmeter (model T/201/PDS). Five animals had drainage catheters inserted into the bladder. The remaining 9 animals had drainage catheters placed in the left and right ureters. After catheterization, the bladder or ureters were allowed to drain by gravity. This accumulation of urine was emptied before initiation of IAB support.

A femoral arterial line was placed through a cutdown. Immediately after insertion, pressure-monitoring lines were connected to pressure transducers (American Edwards Laboratories, Irvine, CA). Pressure tracings along with the electrocardiogram were connected to a PPG Biomedical System model VR-16 (Pleasantville, NY). Mixed venous oxygen saturation and thermodilution cardiac output (CO) were obtained using an Oxymetrix System 3 SVO_2/CO computer (Abbott Critical Care Systems, Mountain View, CA). Baseline hemodynamic measurements were obtained before IAB placement.

A cutdown was then performed on the femoral artery on the side opposite placement of the arterial line, and a 12-mL IAB (Datascope Inc, Paramus, NJ) was inserted

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through the left or right femoral artery depending on randomization. Intraaortic balloon position was randomized so that it was initially placed in either the control or the renal position. For the control position, the balloon was placed between the left subclavian and renal arteries. For the renal position, the middle of the balloon was placed directly over the ostia of the renal arteries. Placement of the IAB was confirmed by palpation for the control and renal positions, and the balloon catheter was marked to designate each of these positions.

Pumping was performed for 4 hours in each position. Using this protocol, each animal acted as its own control. The abdominal incision was then closed. Balloon pumping was performed using a Datascope System 84 console. The IAB was synchronized 1:1 with the animal's heart rate and remained 1:1 for the duration of the study. Helium was used as the drive gas.

Data acquisition was performed using a Modular Instrument Incorporated computer (Malvern, PA) with an XYZ data acquisition program. Data analysis was done on a 386 clone, 25 MHz, 387 co-processor, and 80 MByte hard disk using the XYZ program for data manipulation and SYSTAT statistics program for statistics and graphical output. SYSTAT subroutines were used to evaluate *t* tests, analysis of variance and covariance, regression, correlation, and factor analysis. The eight channels of continuous data (femoral and carotid arterial pressures, right atrial pressure, pulmonary arterial pressure, left and right renal blood flows, mixed venous oxygen saturation, and heart rate) were digitized at 250 samples per second per channel for 6-second epochs every minute. The raw data and resultant computed hemodynamic values were stored every minute, and average values were reported every half hour.

Thermodilution COs, urine output, pulmonary capillary wedge pressure, and blood gases were obtained every 30 minutes. Blood chemistry studies included values for blood urea nitrogen, creatinine, electrolytes, and blood glucose in addition to serum hemoglobin and complete blood counts. Samples were drawn before insertion of the IAB (baseline) and at 4 hours and 8 hours. No anticoagulants were used. At the conclusion of each experiment, the animal was electively sacrificed with sodium pentobarbital. The kidneys were removed from 10 animals, fixed in formalin, and sent for pathological examination.

Results

The IAB was inserted into the left femoral artery in 9 animals and the right femoral artery in 5 animals. It was initially placed in the control position in 8 animals and in the renal position in 6 animals. To determine if placing the IAB in the control or renal position during the first 4 hours or second 4 hours resulted in any differences, we ran a one-way analysis of variance of variables with starting or finishing position as a factor. No significant differences were noted.

Table 1. Hemodynamic Results[a]

Variable	Control Position	Renal Position	*p* Value[b]
Heart rate (beats/min)	137 ± 5	131 ± 4	NS
Carotid artery pressure (mm Hg)			
Systolic	126 ± 3	134 ± 4	NS
Diastolic	80 ± 2	91 ± 3	0.01
Mean	107 ± 2	113 ± 4	NS
Femoral artery pressure (mm Hg)			
Systolic	129 ± 6	154 ± 5	0.003
Diastolic	69 ± 3	64 ± 4	NS
Mean	97 ± 3	110 ± 4	0.014
Cardiac index ($L \cdot m^{-2} \cdot min^{-1}$)	4.2 ± 0.3	4.2 ± 0.4	NS
Total renal blood flow (mL/min)	229 ± 20	182 ± 21	NS
Left renal blood flow (mL/min)	108 ± 5	83 ± 4	0.001
Right renal blood flow (mL/min)	121 ± 5	99 ± 6	0.003
Renal blood flow in 9 occluded vessels (mL/min)	105 ± 11	48 ± 14	0.005
Total urine output (mL/h)	28 ± 3	20 ± 2	0.009
Right atrial pressure (mm Hg)	8 ± 1	7 ± 2	NS
Pulmonary capillary wedge pressure (mm Hg)	8 ± 1	7 ± 1	0.001
SaO_2 (%)	99 ± 1	100 ± 0.1	NS
SVO_2 (%)	89 ± 1	89 ± 1	NS

[a] Data are shown as the mean ± the standard error of the mean. [b] Significance was assessed using unpaired *t* test.

NS = not significant; SaO_2 = arterial oxygen saturation; SVO_2 = mixed venous oxygen saturation.

In 8 animals, at least one of the renal arteries was partially occluded (>20% decrease in flow) while the IAB was in the renal position, the decrease in renal blood flow ranging from 23% to 98% (mean decrease, 66%). In 1 animal, both renal arteries were partially occluded (36% and 82%). While the balloon was in the renal position, nine (seven left and two right) of 28 renal arteries were partially occluded. There was no relationship between the side of IAB insertion and the side of renal artery occlusion.

There were no significant differences between baseline and control position hemodynamics. Hemodynamics with the balloon in the control and renal positions are shown in Table 1. The carotid arterial diastolic, femoral arterial systolic, and femoral arterial mean pressures were all significantly higher when the IAB was in the renal position.

Total renal blood flow was lower while the IAB was in the renal position, but this did not reach significance. While the balloon was in the renal position, there were significantly lower left and right renal blood flows (Fig 1) and urine output. Figure 2 shows the renal blood flow in

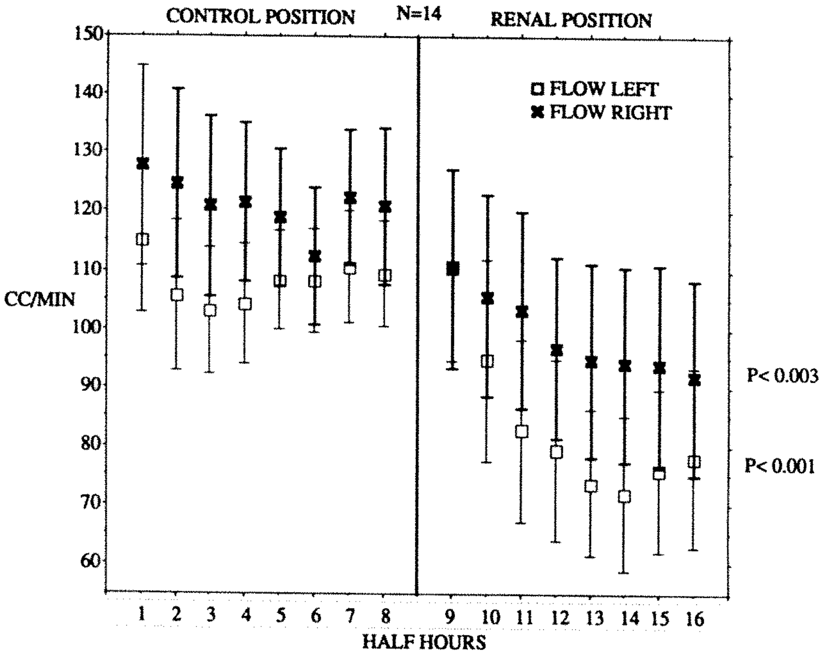

Fig 1. Comparison of left and right renal blood flows with the intraaortic balloon in the control and renal positions. The p *values represent unpaired* t *test on the means for position.*

the partially occluded vessels while the balloon was in the control and renal positions. In the vessels, renal blood flow was significantly lower while the balloon was in the renal position compared with the control position. Partial occlusion occurred only while the IAB was in the renal position. The pulmonary capillary wedge pressure was significantly lower with the IAB in the renal position. There were no significant differences in any of the other hemodynamic variables measured.

In 9 animals, the left and right ureters were catheterized. The urine output from eight kidneys with partial renal artery occlusion is shown for both the control and renal positions in Figure 3. While the IAB was in the renal position, there was virtually no urine output from the kidneys with partially occluded renal arteries ($p < 0.0001$).

Hematological data for the control and renal positions are shown in Table 2. There were no significant differences in any of these variables.

Twenty of 28 kidneys were available for pathological examination. Eight kidneys were not examined. Seven of the 20 kidneys had renal artery occlusion. Five of the seven kidneys with occlusion had mild glomerular ischemic obsolescence, one had moderate ischemic obsolescence, and one had early acute tubular necrosis as a result

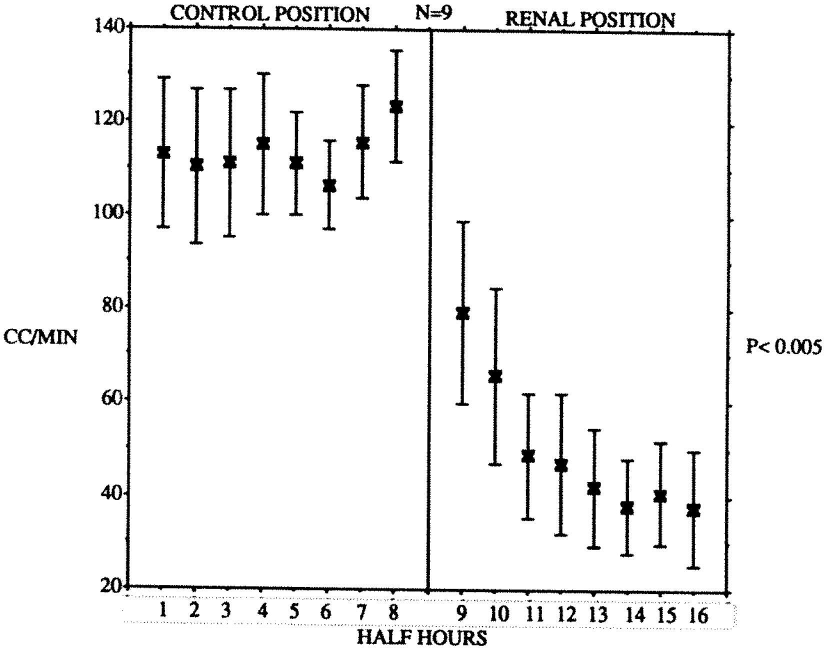

Fig 2. Renal blood flow in vessels that were partially occluded (renal position only) with the intraaortic balloon in the control and renal positions. The p *values represent unpaired* t *test on the means for position.*

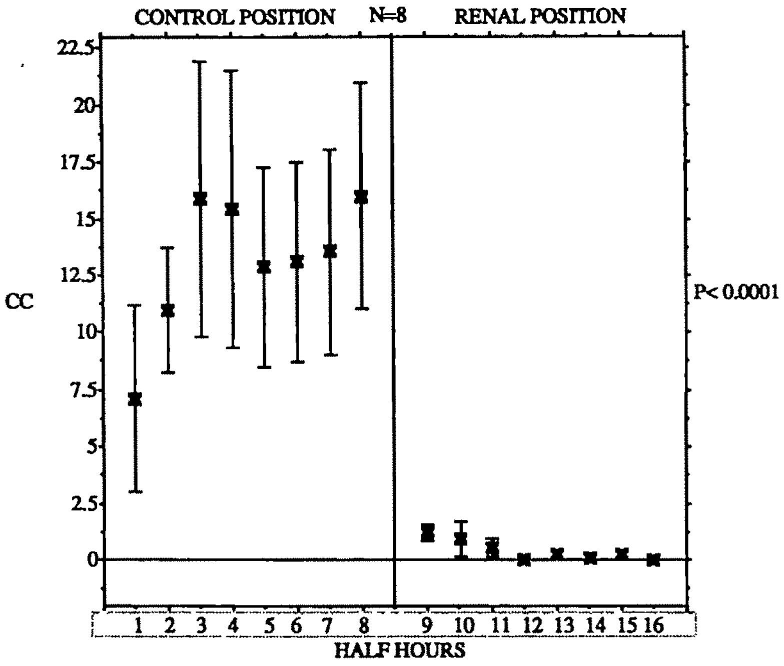

Fig 3. Urine output from kidneys with partially occluded vessels (renal position only) with the intraaortic balloon in the control and renal positions. The p values represent unpaired t test on the means for position.

of a recent thrombus to a large lobar artery. The remaining 13 kidneys had mild ischemic obsolescence of the glomeruli (n = 7) or no pathological diagnosis (n = 6).

Comment

The purpose of this study was to evaluate what effects placing an IAB in the abdominal aorta would have on renal blood flow. Maximal effectiveness of IAB pumping occurs when the inflated volume of the IAB is equal to or not more than 5 mL greater than left ventricular stroke volume [2]. When inflated, most currently used balloons (40 mL) occlude or nearly occlude the aorta. Therefore, to increase the size of balloons to volumes closer to normal left ventricular stroke volumes (60 mL), it would be necessary to increase the length rather than the diameter of the balloon. This would necessitate placement of part of the balloon in the ascending or abdominal aorta. Animal studies [2] have documented that placement of an IAB in the thoracic aorta between the left subclavian and the renal arteries results in the best overall effects, as the augmentation of coronary flow is optimized if there is a blood compartment between the IAB and the heart. Placement of a balloon in the ascending aorta results in the greatest reduction in systolic left ventricular pressure [1], but data from our laboratory show that the ascending aortic position has several disadvantages, including possible cerebral embolization and difficulty keeping the balloon in the correct position. For these reasons, it seemed reasonable to extend the length of the IAB into the abdominal aorta rather than the ascending aorta.

Table 2. Hematological Results[a,b]

Variable	Control Position	Renal Position
Blood urea nitrogen (mg/dL)	15 ± 1	17 ± 0.9
Creatinine (mg/dL)	0.7 ± 0.05	0.7 ± 0.05
Sodium (mmol/L)	149 ± 1	148 ± 0.7
Potassium (mmol/L)	4.0 ± 0.1	4.1 ± 0.1
Chloride (mmol/L)	117 ± 0.9	117 ± 0.9
CO_2 (mmol/L)	22 ± 0.9	23 ± 0.7
Blood glucose (mg/dL)	80 ± 4	74 ± 5
Serum hemoglobin (mg/dL)	19 ± 2.5	15 ± 2

[a] Data are shown as the mean ± the standard error of the mean. [b] Significance was assessed using unpaired *t* test, and no significant differences were found.

In a pilot study, we determined that a 12-mL IAB occluded approximately 80% to 90% of the thoracic aorta in dogs weighing 20 to 25 kg. We recognize that the abdominal aorta of a dog is narrower than the thoracic aorta and that in some of these animals, the abdominal aorta appeared to be totally occluded by the IAB. During postmortem examinations of the animals sacrificed while the IAB was in the renal position (n = 8), 2 appeared to have totally occluded aortas when the IAB was inflated. In spite of this, in all the experiments, blood flow distal to the IAB was adequate, as demonstrated by femoral arterial pressure tracing (Fig 4), warm extremities, and lack of acidosis. Aortic occlusion obviously occurs in some humans, as the same-sized IAB (40 mL) is often placed in patients weighing 50 to 100 kg. In these experiments, the decrease in renal blood flow while the IAB was in the renal position was due to partial and selective renal artery occlusion, not bilateral occlusion as would be expected from an oversized IAB.

Numerous clinical complications have been associated with IABs [4–9]. These complications include renal failure, small-bowel infarction, and paraplegia, all of which could

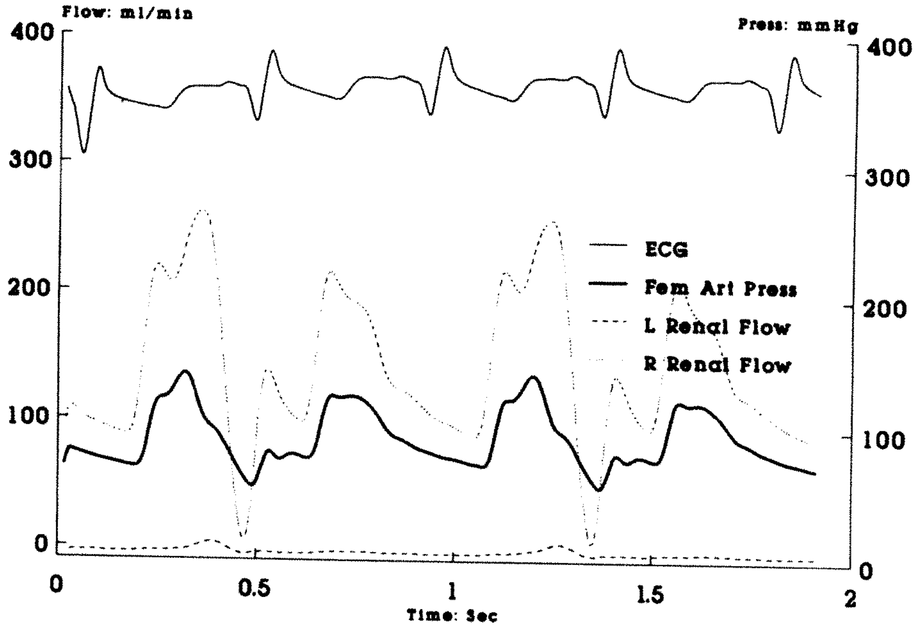

Fig 4. Electrocardiogram (ECG), *femoral arterial pressure, and left and right renal blood flows with the intraaortic balloon in the renal position at a pumping ratio of 1:2.*

result from partial or total obstruction of a branch off the aorta [10–13]. Hilberman and associates [10] presented the cases of 2 patients who had IABs positioned adjacent to the ostia of the renal arteries. In 1 patient, repositioning the balloon to the correct position improved renal function. In the other, the balloon was not repositioned, and renal failure developed. Renal failure directly attributed to IAB position is rare; however, many of the complications related to IABs are not discovered until postmortem examination. A review [8] of the autopsy records of 45 patients who died after insertion of IABs showed 16 (36%) had one or more complications related to use of the IAB. Of the 20 complications, only four (20%) were suspected before death.

Intraaortic balloon pumping in the thoracic aorta in animals in cardiogenic shock increases renal blood flow from 9% to 29.8% [2, 14]. The exact percentage of increase of renal blood flow in humans in cardiogenic shock is not known. Clinically, it seems that renal perfusion is enhanced by an IAB. In theory, placement of an IAB adjacent to the renal arteries could decrease renal perfusion; however, IABs positioned "too low" may have no effect on renal function [6]. In this study, if we had not had continuous measurements of renal blood flow, we would not have been able to identify the high incidence of renal artery occlusion. A comparison of the traditionally monitored hemodynamics obtained during the control and renal periods gives no indication of a reduction in renal perfusion. Heart rate, cardiac index, mixed venous oxygen saturation, and right atrial pressure measurements were not significantly different from control values while the IAB was in the renal position (see Table 1). Carotid artery diastolic, femoral artery systolic, and femoral arterial mean pressures were all significantly higher while the IAB was in the renal position. The etiology of these higher arterial pressures is unknown but may be related to a decrease in renal blood flow or renal vasoconstriction. In any case, an increase in systemic pressure in a patient with a stable and adequate cardiac index and in cardiogenic shock would probably lead to a reduction in inotropic support or an increase in vasodilator therapy or both. The pulmonary capillary wedge pressure was significantly lower while the IAB was in the renal position (7.53 ± 0.22 control versus 6.53 ± 0.20 renal; $p < 0.001$). However, this difference is not clinically significant.

During these experiments, urine output was lower while the balloon was in the renal position compared with the control position. Decreasing urine output is one of the first indicators of renal dysfunction or hypoperfusion. This is especially true in patients in acute cardiogenic shock. A decrease in urine output with stable hemodynamics is not unusual in such patients. A decrease in urine output may initially be treated with diuretics, volume loading, or increased inotropic support. A clinical scenario similar to these experiments may not produce any change in hemodynamics or blood chemistry values during the initial 4 to 6 hours. Once a progressive rise in creatinine and blood urea nitrogen levels as well as a decrease in urine output was documented, an irreversible lesion may have developed. In this study, there was no change in blood urea nitrogen and creatinine levels during the 4-hour period while the balloon was in the renal position. In patients with acute renal artery occlusion, blood urea nitrogen and creatinine levels may be normal or only slightly elevated for up to 1 week [15–17]. Although some patients may tolerate loss of one kidney fairly well, patients in cardiogenic shock with IABs would not tolerate losing 50% of their already impaired renal function.

Acute renal artery occlusion is difficult to diagnose clinically. Symptoms include persistent abdominal pain, fever, nausea, vomiting, anorexia, and back or flank pain [15–17]. Similar symptoms are encountered with pancreatitis, cholecystitis, dissecting abdominal aortic aneurysm, retrocecal appendicitis, pancreatic pseudocyst, pelvic inflammatory disease, and acute ureteral obstruction. All of these are more common than acute renal artery occlusion. The pain associated with pulmonary infarction, pneumonia, and myocardial infarction is also similar to the pain seen in patients with acute renal artery occlusion [15]. As many as 25% of patients with renal artery occlusion may have no pain at all [16, 17].

Complete renal artery occlusion results in a loss of renal function; however, collateral flow may be sufficient to preserve kidney viability [18, 19]. Collateral blood flow at subfiltration pressures may preserve the glomerulus for a while, but irreversible renal tubular atrophy and acute tubular necrosis are likely if total occlusion persists longer than 4 hours [20]. In these experiments, there was not a total loss of renal blood flow; therefore, the affected kidneys remained viable yet virtually nonfunctional. Only one kidney had necrosis, which was due to thrombotic occlusion, probably a result of low flow and no anticoagulation. Anticoagulation might have prevented the thrombus; however in this renal artery, the flow was reduced by 82% while the IAB was in the renal position. In addition, systemic heparinization with this animal model would have probably led to bleeding complications and the need of transfusion. This was the only instance where the reduction in renal blood flow was due to thrombus. In all other instances, the obstruction was mechanical in nature and due to the obstruction of the ostia of the renal arteries by the IAB. The pathological examination of the remaining kidneys showed mild to moderate ischemia or no damage. Seven kidneys with no decrease in renal blood flow also had mild ischemic changes, a finding suggesting that, at least in this study, the pathology was not very useful in determining the acute deleterious effects of reduced renal blood flow. The 4-hour period was inadequate to document significant renal injury by pathological findings. Longer intervals of IAB pumping might have provided more convincing pathological results, but this was unnecessary, as the renal blood flow and urine output measurements clearly showed renal insufficiency while the IAB was in the renal position. Several kidneys with ischemia and little or no urine output began making more urine when the IAB was moved from the renal to the control position. This suggests that the injury was readily reversible once the occlusion was relieved and normal renal blood flow restored.

The lowest renal blood flow was in the partially occluded vessels while the IAB was in the renal position (see Table 1). The renal blood flow in these occluded vessels was 47.5 ± 13.5 mL/min or 1.33% of the CO. Total renal blood flow in dogs in cardiogenic shock and IABs in the conventional (control) position has been estimated at 13.39% ± 2.02% of the CO [14]. In the presence of cardiogenic shock and IAB support in dogs, each kidney receives approximately 6% of the CO. Therefore the occluded kidneys in this study received only 25% of the available blood flow that a kidney of a dog in cardiogenic shock should have received. Because the animals in this study were not in cardiogenic shock, the reduction in renal blood flow is much more dramatic.

Clinically, many IABs are inserted without the aid of fluoroscopy. This is especially true for balloons placed in the operating room during cardiac surgical procedures or in the intensive care unit during emergency situations. For these cases, balloon position is confirmed by chest roentgenograms some time after implantation. This study shows that if a balloon is determined to be too low (adjacent to the renal arteries), it should be advanced. If there is any question of balloon position, radiopaque material can be injected through the central lumen of the balloon during fluoroscopy.

Figure 4 shows the renal blood flow characteristics in an occluded vessel and a nonoccluded vessel during several cardiac cycles with the IAB in the renal position at a pumping ratio of 1:2. This tracing was obtained after the experiment had been concluded. Partial renal artery obstruction can occur while the IAB is either inflated or deflated, functioning or nonfunctioning.

This study demonstrates that selective renal blood flow was significantly lower when an IAB was in the renal versus the control position. This was due to a mechanical obstruction that occurred when the IAB occluded the renal artery ostia. The reduction in renal blood flow cannot be diagnosed using conventional monitoring techniques.

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Effect of Cardiopulmonary Bypass on Circulating Lymphocyte Function

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Extracorporeal cardiopulmonary bypass (CPB) has been associated with a wide variety of immunological derangements, including a transient postoperative impairment of lymphocyte function. We examined changes in phenotypic and nonspecific cytotoxicity of peripheral blood mononuclear cells after extracorporeal CPB. The peripheral blood samples obtained from 10 patients were subjected to natural killer and cytotoxic T lymphocyte activity assay before and at intervals after CPB. Phenotypic analysis of peripheral blood lymphocytes was performed in 5 patients before and immediately after CPB. We observed a significant increase in peripheral blood CD8+ cells (cytotoxic/suppressor T lymphocytes) (16.1% ± 2.5% versus 22.5% ± 2.1%; $p < .005$) and a decrease in CD4+ cells (helper/inducer T lymphocytes) (46.1% ± 3.5% versus 36.1% ± 3.5%; $p < 0.02$) immediately after extracorporeal circulation. The CD8/CD4 ratio in peripheral blood was significantly increased immediately after bypass (0.53 versus 0.80; $p < 0.001$). No significant changes in percentages of other leukocyte subsets in peripheral blood were noted. The activity of cytotoxic T lymphocytes and natural killer cells in peripheral blood was impaired on postoperative days 1 and 3 but was restored to preoperative values by removal of mononuclear phagocytes from these cells. The decrease in natural killer cell and cytotoxic T lymphocyte activity in peripheral blood may signify a temporary impairment of the effector arm of the cell-mediated immunity in the postoperative period. The observed changes in peripheral blood phenotype and function may be involved in early organ injury and infectious complications after CPB.

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Cardiac surgical intervention employing extracorporeal cardiopulmonary bypass (CPB) is one of the most frequently performed procedures in North America [1]. Overall, it is a relatively safe operation with a postoperative morbidity of approximately 5% and a mortality of close to 2% [2–4]. Cardiopulmonary bypass has been found to be associated with a wide variety of early postoperative physiological and immunological derangements, including an observed increase in capillary permeability, and interstitial fluid, mild fever, leukocytosis, bleeding diathesis, and hepatic, cardiac, pulmonary, and renal dysfunction with a wide spectrum of severity [5–8]. The pathogenesis of these changes is complex and is thought to depend in part on leukocyte margination and tissue sequestration with complement, neutrophil, and cytotoxic T cell activation and release of inflammatory mediators causing widespread endothelial injury [5].

Both humoral and cell-mediated immunity have been shown to be adversely affected for a short period after CPB. For instance, neutrophil functions that are relevant to antibacterial host defenses, such as chemotaxis and bactericidal activity, were shown to be depressed [9, 10]. Furthermore, the in vitro proliferative response of lymphocytes, an important component of the host antiviral defenses, was noted to be markedly impaired for a variable period after CPB [11, 12]. The transient postoperative immunodeficient state may result in an increased risk of infectious complications after CPB.

In this study, we examined the effect of CPB on (1) the phenotypes of circulating leukocytes using standard commercially available leukocyte-labeling monoclonal antibodies and (2) the immunological function of circulating lymphocytes using in vitro cytolytic assays. Specifically, we studied natural killer (NK) and cytotoxic T lymphocyte (CTL) cytolytic activity in peripheral blood mononuclear cells isolated before and at various intervals after CPB. These cytotoxic functions represent an important component of the cell-mediated immunity. Functional cytolytic assays can directly assess the influence of cardiac procedures with CPB on the effector arm of the cell-mediated immune system.

Material and Methods

Ten consecutive patients (8 men and 2 women) undergoing a cardiac operation with CPB for atherosclerotic coronary artery disease (n = 8) and valvular heart disease (n = 2) were studied. The mean age was 61.8 years (range, 34 to 78 years). All preoperative hemograms and liver and kidney function profiles were normal. Average stay in the hospital after operation was 8.5 days (range, 7 to 11 days). There were no major postoperative infectious complications. Informed consent was obtained before operation, and the study was approved by the Human Research

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Advisory Board of The Montreal General Hospital and McGill University.

Extracorporeal CPB was performed with a Bentley 10 plus oxygenator, Tygon and silicone tubing, a BCR cardiotomy reservoir, and an AF-1025 arterial filter. Two liters of Ringer's lactate solution containing 44 mEq of bicarbonate and 12.5 g of mannitol was used to prime the pump oxygenator. The average bypass time and total operating time were 107 minutes (range, 63 to 158 minutes) and 237 minutes (range, 180 to 310 minutes), respectively. Blood lost was replaced with packed red blood cells buffered with citrate-phosphate-dextrose. All patients were given cefazolin sodium as a prophylactic antibiotic. Complete blood counts with automatic differential leukocyte counts by a Coulter counter were recorded daily for 7 days after operation.

Samples of heparinized peripheral venous blood were obtained from each patient before induction of anesthesia, 15 minutes after termination of extracorporeal CPB, and on postoperative days 1, 3, and 7. Mononuclear cells were isolated from peripheral blood by the Ficoll-Hypaque (Pharmacia, Piscataway, NJ) density-gradient technique (specific gravity, 1.007) as outlined by Pharmacia. Mononuclear cells were washed twice and then suspended in RPMI 1640 medium supplemented with penicillin (100 IU/mL), streptomycin (100 μg/mL), glutamine (2 mmol/L), and 5% fetal calf serum (RPMI complete). Cells were adjusted to the appropriate concentration (5×10^6/mL) for cytolytic assays. Total cell counts were performed manually with an improved Neubauer hemocytometer using 1% acetic acid as the counting fluid. Slide preparations were made in a cytocentrifuge using 100-μL aliquots (5.0×10^5 cells) of the mononuclear cell suspensions and spun at 500 rpm for 5 minutes. A differential count was made from total counts of 300 cells using a leukostat stain kit (Fisher Scientific, Orangeburg, NY) and a nonspecific esterase stain (Sigma Diagnostic, St. Louis, MO) to better differentiate monocytes from lymphocytes.

Mononuclear cells obtained preoperatively and 7 days after operation contained 85% to 90% lymphocytes, whereas those obtained on postoperative days 1 and 3 contained only 45% to 50% lymphocytes. The remaining cells were monocytes. The monocytes were removed from mononuclear cells isolated on postoperative day 3 by the plastic-adhering technique described elsewhere [13]. Nonadhering cells (90% of which were lymphocytes) were adjusted to an appropriate concentration and assayed in parallel with their original mononuclear populations for NK and CTL activity to study the role of circulating monocytes in the observed changes in lymphocyte cytotoxic function after extracorporeal CPB.

Phenotypic Analysis of Peripheral Blood Lymphocytes

In 5 patients, heparinized venous blood samples were collected immediately before and at the termination of CPB. Peripheral blood mononuclear cells were similarly isolated by Ficoll-Hypaque gradient centrifugation. Cells were washed in phosphate-buffered saline solution and aliquots of 5×10^5 cells were incubated with fluorochrome-conjugated monoclonal antibodies (Becton-Dickinson, Mountain View, CA) as follows:

Anti-Leu 2a (CD8): T cytotoxic/suppressor cell
Anti-Leu 3a (CD4): T helper/inducer cell
Anti-Leu 4 (CD3): T cell (mitogenic)
Anti-Leu 7 (—): T cell and NK cell subsets
Anti-Leu 8 (—): T cells, B cells, neutrophils, monocytes
Anti-Leu 11 (CD16): FcIgG receptor on NK cells, neutrophils
Anti-Leu 12 (CD19): B cells
Anti-Leu MS (—): Monocytes/macrophages
Anti-HLA-DR (—): B cells, monocytes, macrophages, activated T cells

Flow cytometric analysis was performed using a fluorescence-activated cell analyzer and a Consort 30 computer system (Becton-Dickinson). Cell populations were identified, and data are presented as percentages of gated lymphocytes.

Natural Killer Cell Cytolytic Assay

The NK cell cytotoxicity was measured by the 4-hour chromium 51–release assay using the K562 cell line as target. An appropriate number of effector cells was added to a fixed number (10^4) of ^{51}Cr–labeled target cells in a round-bottom 96-well tissue culture plate at effector to target ratios of 50:1, 25:1, and 12.5:1. Assays were done in triplicate. After incubation at 37°C in humidified air with 5% carbon dioxide for 4 hours, the culture plates were centrifuged at 400 *g* for 5 minutes. From each well, 100 μL of supernatant was harvested, and radioactivity was estimated in a gamma scintillation counter. The NK cell cytotoxicity, expressed as percent cytolysis, was calculated by a standard formula using the mean values of triplicate cultures:

$$\%\text{Cytolysis} = (\text{CPM experimental}$$
$$- \text{CPM spontaneous release})/(\text{CPM total release}$$
$$- \text{CPM spontaneous release}) \times 100,$$

where CPM = count per minute. Spontaneous release was determined in wells containing labeled target cells and medium alone. Total release was determined by incubating labeled target cells with 100 μL of 0.5% Triton X100 detergent. Spontaneous release was always less than 5% of total release.

Lectin-Dependent Cell-Mediated Cytotoxicity Assay

The Raji cell line (a human lymphoblastoid cell) served as the target. It was similar to the NK assay with the addition of the lectin concanavalin A to the assay medium to a concentration of 8 μg/mL. This assay is regarded as a quantitative measurement of CTL activity. The effector cells in this assay are thought to be preexisting circulating lymphocytes activated against a variety of antigenic stimuli encountered daily by the individual [14].

Statistical Analysis

Results are presented as the mean ± the standard error of the mean. Data were analyzed using repeated-measures

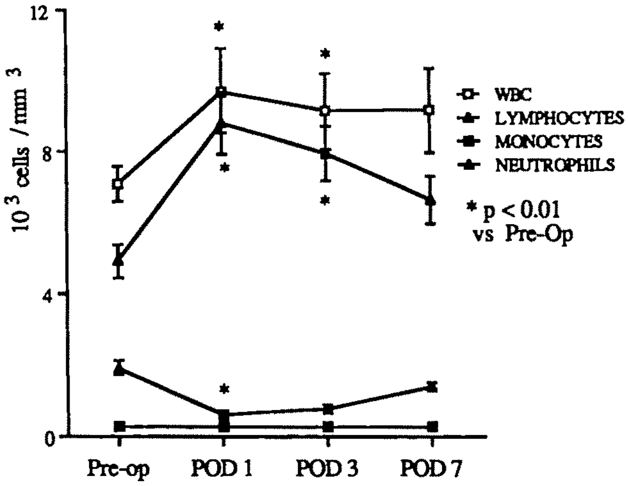


Fig 1. Total and differential counts of peripheral blood leukocytes before and at intervals after cardiopulmonary bypass. Neutrophilia accounted for the early postoperative leukocytosis. Total lymphocyte count was significantly lower than normal immediately after operation. It then gradually returned to the preoperative value. The number of circulating monocytes was unchanged throughout the postoperative period. (POD = postoperative day; WBC = white blood cells.)

Table 1. Cytotoxic/Suppressor and Helper/Inducer T Lymphocyte Subsets Before and Immediately After Cardiopulmonary Bypass[a]

Subsets	Before	After
CD8 (%)	16.1 ± 2.5	22.5 ± 2.1[b]
CD4 (%)	46.1 ± 3.5	36.1 ± 3.5[c]
CD8/CD4	0.53	0.80[d]

[a] Where applicable, data are shown as the mean ± the standard error of the mean. A paired t test determined significance. [b] Significance: $p < 0.05$. [c] Significance: $p < 0.02$. [d] Significance: $p < 0.001$.

analysis of variance. Statistical difference between pairs of means was then determined by the Bonferroni test. Changes in lymphocyte phenotypes before and after CPB were compared using a paired t test, and a p value of less than 0.05 was considered significant.

Results

A modest but significant increase in the postoperative leukocyte count was observed (7.1 ± 0.5 × 10^9/L [7,100 ± 500/μL] before CPB versus 9.7 ± 1.2 × 10^9/L [9,700 ± 1,200/μL] on postoperative day 1; $p < 0.02$). This was attributed primarily to an increase in the absolute neutrophil count (4.9 ± 0.4 × 10^9/L [4,900 ± 400/μL] before CPB versus 8.8 ± 1.1 × 10^9/L [8,800 ± 1,100/μL] on postoperative day 1; $p < 0.01$). This elevation in the leukocyte count was observed up to day 7 after operation. Lymphopenia was observed on postoperative days 1 and 3, with a gradual return to normal levels on postoperative day 7. The absolute count of mononuclear phagocytes (MNP) in peripheral blood was unchanged throughout the study period (Fig 1). These changes reduced the lymphocyte to MNP ratio in our assays from 5.7:1 before operation to 1.7:1, 2.8:1, and 5.1:1 on days 1, 3, and 7 after operation, respectively.

Extracorporeal CPB was associated with an immediate elevation in the percentage of CD8+ lymphocytes in peripheral blood (16.1% ± 2.5% before CPB versus 22.5% ± 4.1% after CPB; $p < 0.05$). This increase in the percentage of suppressor/cytotoxic cells was accompanied by a reduction in the proportion of helper/inducer (CD4+) lymphocytes (46.1% ± 7.2% before CPB versus 36.1% ± 5.2% after CPB; $p < 0.02$). These changes resulted in a significant increase in the CD8/CD4 ratio (0.5 before CPB versus 0.8 after CPB; $p < 0.001$) (Table 1).

Peripheral blood NK cell activity expressed as percent cytolysis at an effector to target ratio of 50:1 was unchanged 15 minutes after termination of CPB (cytolytic activity of 36.1% ± 2.6% before CPB versus 39.0% ± 2.5% after CPB; p = not significant) (Fig 2). However, it was significantly reduced on postoperative days 1 and 3 (20.3% ± 2.6% and 19.0% ± 3.0%, respectively; $p = 0.001$

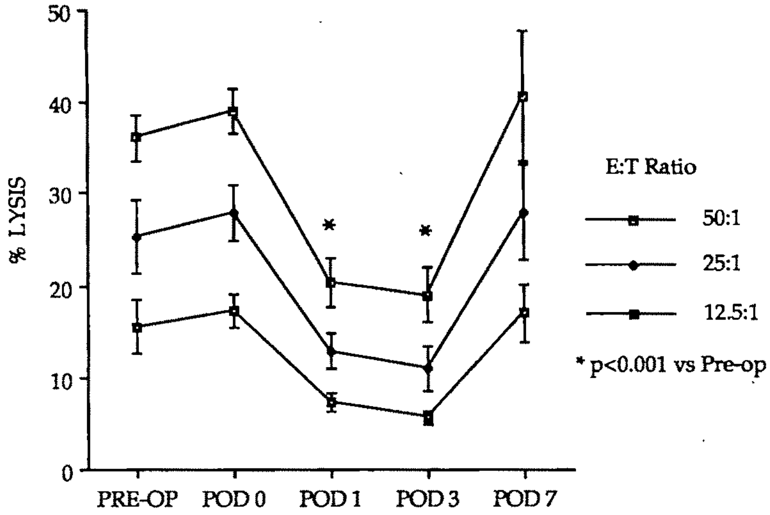
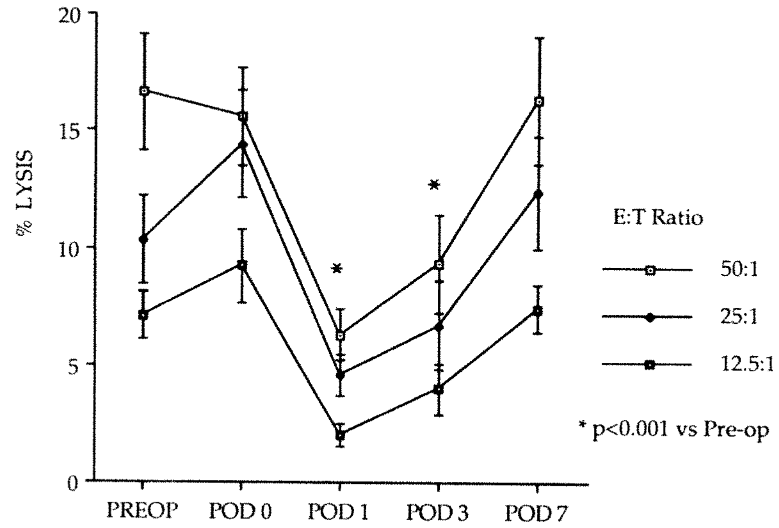


Fig 2. Natural killer (NK) cell cytolytic activity in peripheral blood in the early postoperative period at three effector to target (E:T) ratios. Reduction of NK activity was most pronounced on postoperative days (POD) 1 and 3. However, the impairment of NK cell function was self-limited; it returned to normal by postoperative day 7.

Fig 3. Cytotoxic T lymphocyte cytolytic activity in peripheral blood in the early postoperative period at three effector to target (E:T) ratios. Like the natural killer cell, cytotoxic T lymphocyte activity was significantly lower in the early postoperative period. Cytotoxic T lymphocyte activity was measured by the lectin-dependent cell-mediated cytotoxicity assay. (POD = postoperative day.)



versus preoperative value). Natural killer cell activity was slightly higher on postoperative day 7, but the difference was not significant (40.7% ± 7.1% versus 36.1% ± 2.6% before CPB; $p = 0.15$).

Cytotoxic T lymphocyte activity showed serial changes similar to those of NK cells in the postoperative period. Lymphocyte cytolytic activity was lowest on postoperative day 1 (6.3% ± 1.1% versus 16.6% ± 2.5% before CPB; $p = 0.001$), started returning to the baseline value (measured before CPB) on day 3 after operation, and attained the baseline level on postoperative day 7 (Fig 3).

Interestingly, the decrease in NK activity seen 3 days postoperatively was reversed by removal of plastic-adhering MNPs (19.0% ± 3.0% before removal of MNPs and 35.8% ± 4.3% after removal of MNPs versus the baseline value of 36.1% ± 2.6%) (Fig 4). The impaired CTL activity observed on postoperative day 3 was similarly restored to the control value by removal of MNPs.

Comment

A variety of subtle immunodeficiencies after surgical procedures have been described. It has been suggested that the use of extracorporeal circulation adversely affects a wide range of host defense mechanisms. Both humoral and cell-mediated immune systems have been shown to be impaired after open heart operation. Neutrophil chemotaxis and intracellular bactericidal activity have been found to be impaired postoperatively for at least 5 days [9, 10]. Profound lymphopenia, caused mainly by a drastic reduction in helper/inducer lymphocytes (CD4+ cells), occurred within 24 hours and lasted 3 to 4 days after operation [15, 16]. The remaining circulating lymphocytes were functionally impaired and responded poorly to mitogen and to alloantigen stimulations in vitro [11, 12]. Moreover, immunoglobulin synthesis and secretion by B lymphocytes were found to be transiently impaired after operation with CPB [17]. Anaphylatoxins generated by complement activation after CPB were thought to play an important role in the damaging effects of this procedure [18, 19].

These findings may indicate that postoperatively, lymphocytes temporarily lose their ability to respond to challenging antigens as well as to initiate a specific cell-mediated immune response. There is circumstantial evidence of a cell-mediated or humoral inhibitory factor (or factors) responsible for the observed postoperative lymphocyte hyporesponsiveness, as normal lymphocytes have lost their strong proliferative responses to mitogens when cultured either in plasma collected from patients after operation or with postoperative peripheral blood mononuclear cells [20]. Cardiac surgical procedures seem

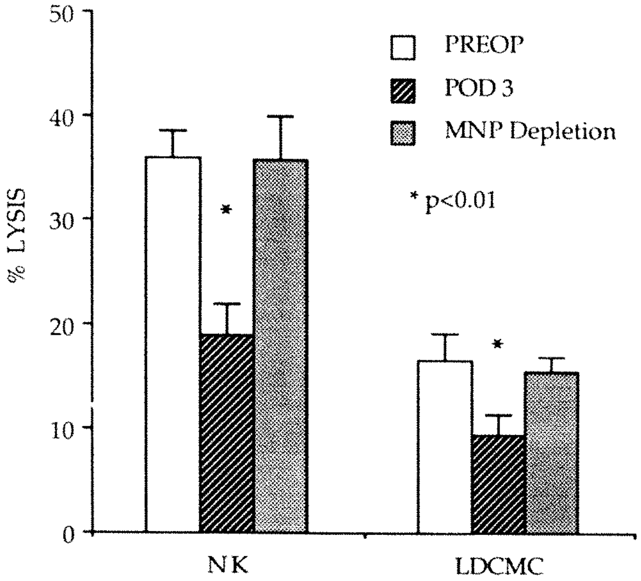


Fig 4. Restoration to normal levels of natural killer (NK) and lectin-dependent cell-mediated cytotoxicity (LDCMC) activity on postoperative day (POD) 3 by removal of mononuclear phagocytes (MNP) from the effector cell population.

to be associated with a longer and more profound impairment of the immune system than other operative procedures [20]. With the advent of balloon angioplasty and better medical management of patients with coronary artery disease, older and sicker patients are being referred for operation. If cardiac operations indeed result in a significant immune dysfunction as identified in this study and others, it would be important to document whether such basic defects are associated with a concurrent increase in the incidence of infection and hence the need for specific prophylaxis or other methods to augment the host immune mechanisms after cardiac surgical procedures.

The reduction of NK cell cytotoxicity in vitro after cardiac operations has previously been described [21, 22]. It was found to occur within 15 minutes of the termination of CPB, last for 3 to 4 days, and return to the preoperative level on day 7 after operation. Our data agree with this observation with only the minor difference that there was no change in the NK activity 15 minutes after completion of CPB. In our in vitro study of the cytolytic activity of preexisting circulating CTLs after cardiac operations, we found that the serial postoperative changes in the lectin-dependent cell-mediated cytotoxicity assay paralleled those of the NK activity. Investigation of lymphocyte functions after operation using an in vitro cytolytic assay could allow direct assessment of the influence of operation on the effector arm of the immune system. These preexisting circulating effector cells will be the first ones to encounter pathogens (eg, virus-infected cells and viral or fungal particles) and to destroy them. The impairment of the cytolytic function of these effector cells truly reflects an immunocompromised state postoperatively.

We observed an early increase in the percentage of CD8+ cells and in the CD8/CD4 ratio immediately after CPB. As lymphopenia was also noted after bypass, it is likely that the absolute CD4+ cell counts were affected more than the CD8+ cell counts. This may be due to a direct effect of the CPB machine or an indirect effect through the specific sequestration of CD4+ cells in the peripheral circulation and tissue. We have not, however, examined CD11/CD18 receptor levels in circulating leukocytes after CPB. The plausible role of leukocyte margination and adherence on the alteration of circulating lymphocyte phenotypes remains to be defined. The question now is whether the reduction of the cytotoxic activity of postoperative lymphocytes is caused by an actual functional impairment of the effector cells (ie, NK cells and CTLs) or simply by a decrease in their absolute number in the mononuclear cells in the in vitro assay.

The decreased NK and CTL activity coincided with the postoperative lymphopenia. It has been shown that there is a reduction of both cytotoxic (T8) and inducer (T4) lymphocytes and of NK cells in peripheral blood after cardiac operations. Moreover, we observed that mononuclear cells isolated 1 and 3 days postoperatively actually contained only half the number of lymphocytes in the preoperative samples. Therefore, the total number of lymphocytes in cytolytic assays varied with time even when the number of mononuclear effector cells remained unchanged. Alterations in NK and CTL percent cytotoxicity corresponded closely to changes in lymphocyte number in the in vitro assay system; for instance, the NK activity of the effector cells 3 days after operation without MNP depletion (19.0% ± 3.0%) was about half that in the preoperative blood samples (36.1% ± 2.6%). This observation is of importance considering that only 45% to 50% of mononuclear effector cells isolated 3 days after operation were lymphocytes (about half the percentage of lymphocytes in the preoperative effector cell population: 85% to 90%). The same observation was made for CTL activity; for instance, the percent cytotoxicity 3 days postoperatively was equal to half the preoperative level (see Fig 4). It is conceivable that the decreased cytotoxic activity was secondary to a reduction in the total number of lymphocytes in the assay. The remaining cells were functionally intact, as correction of the number of lymphocytes to the preoperative value by removal of adhering cells (mainly MNPs) restored the percent cytotoxicity to baseline levels.

On the other hand, even if the T cell numbers in cultures were adjusted to a constant value, postoperative T-cell mitogenic and antigenic proliferative responses were still depressed, which is a sign of functional impairment of T lymphocytes [11, 12]. Miyazaki and colleagues [13] demonstrated that the de novo generation of cytotoxic lymphocytes in a mixed lymphocyte culture system against a constant target cell was impaired after major surgical procedures. Removal and repletion of postoperative adhering cells (MNPs) respectively abrogated and reconstituted the observed impairment, suggesting that circulating monocytes have an inhibitory effect on the affector arm of the immune system. It is very likely that inhibitory factors generated by surgical stress selectively suppress lymphocyte ability to respond to antigen stimulation (affector arm of the immune response) but not the cytotoxic function of preexisting effector cells such as NK cells and cytotoxic lymphocytes (effector arm of the immune system). One such inhibitory factor is serum cortisol. A high level of cortisol probably plays an important role in postoperative immunosuppression, yet it is not the only factor in this complex phenomenon [23]. Cortisol affects the postoperative changes in lymphocyte cytolytic function indirectly by inducing lymphopenia. A high level of cortisol has been shown to mediate redistribution of circulating lymphocytes to lymphoid organs and bone marrow [15, 24, 25].

In summary, we demonstrated that patients undergoing an open heart operation showed an early alteration in their circulating lymphocyte phenotypes with an increased expression of CD8+ cells and a decreased expression of CD4+ cells. A transient impairment of the peripheral blood NK and CTL activity was also observed. The mechanism of this reduction is not fully elucidated. Whether this is a true qualitative or a quantitative defect is yet to be determined. Whether such basic impairment will translate into an increased susceptibility to infection in patients undergoing cardiac operation needs to be defined. In addition, the plausible contribution of the change in circulating lymphocyte phenotypes to tissue injury secondary to CPB remains to be examined.

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One-Stage Operation for Treatment After Delayed Diagnosis of Thoracic Esophageal Perforation

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Perforation of the thoracic esophagus can be fatal unless diagnosed promptly and treated effectively. The high mortality with delayed treatment is due principally to an inability to effectively close the perforation and prevent leakage. From 1982 to 1988, 7 consecutive patients (aged 16 to 73 years) were treated after a delayed diagnosis (26 hours to 25 days) of thoracic esophageal perforation. In all patients, the perforation was closed after debridement with total exclusion of the esophagus (T-tube cervical esophagostomy plus absorbable ligatures applied to the esophagogastric junction and the cervical esophagus distal to the esophagostomy). Radical decortication and wide mediastinal and pleural drainage were also done. Nutritional supply was given through a feeding gastrostomy. Antibiotics were administered according to the results of cultures. All patients survived. Continuity of the esophagus was established by removal of the T tube and spontaneous absorption of the ligatures. Endoscopy and esophagography performed 4 weeks after the initial operation showed a well-healed esophagus without stenosis or leakage in all patients. No secondary thoracotomy or esophageal reconstruction was necessary. No dysphagia was noted during follow-up (range, 12 to 50 months; mean follow-up, 23 months). We conclude that primary closure of the perforation and total esophageal exclusion with the use of absorbable ligatures and T-tube esophagostomy can provide a one-stage operation with good results for repair of thoracic esophageal perforation diagnosed late.

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Perforation of the esophagus is an emergency that requires early diagnosis and effective treatment if death or serious prolonged illness is to be avoided. This is well demonstrated by the sharp rise in mortality rates when treatment is delayed. The mortality rate for patients treated in less than 24 hours is near 10%, but it rises sharply to 25% to 40% for those treated later [1–7]. The major reason for this abrupt increase is the rapid development of necrotizing mediastinitis combined with the inability to close the perforation effectively and prevent leakage.

The principle of exclusion has long been applied to the treatment of fistula of the intestinal tract. Johnson and colleagues [8] first described esophageal exclusion for the treatment of esophageal perforation in 1956. Urschel and associates [9] proposed a modified technique in 1974. They performed esophageal exclusion by ligation of the esophagus distal to the perforation with an umbilical tape deep to the vagus nerve in conjunction with a proximal cervical esophagostomy. This procedure, however, has the disadvantages of prolonged discomfort and multiple operations to reestablish the continuity of the esophagus. Popovsky [10] used a double strand of absorbable Dexon to ligate the distal esophagus, making a second thoracotomy for removal of the ligature unnecessary. However, patients had to undergo a second operation to close the cervical esophagostomy.

In this report, we present our experience at Chang Gung Memorial Hospital with a one-stage operation to treat 7 consecutive patients with esophageal perforation diagnosed late. Primary repair of the perforation and total esophageal exclusion by T-tube cervical esophagostomy plus absorbable ligatures on the esophagogastric junction and cervical esophagus distal to the esophagostomy was performed on all of these patients.

Material and Methods

Patient Population

We retrospectively reviewed the charts of 7 consecutive patients with delayed diagnosis (more than 24 hours after initial insult) of thoracic esophageal perforation seen between 1982 and 1988. Patients with perforation of the pharynx and cervical esophagus were not included. Also excluded were patients in whom perforation developed from the use of a Sengstaken-Blakemore tube for bleeding esophageal varices and patients with anastomotic dehiscences after elective esophagectomy.

There were 5 male and 2 female patients (Table 1). Age at the time of insult ranged from 16 to 73 years (mean age, 47.1 ± 18.4 years [± standard deviation]). All the esophageal perforations were confirmed by esophagograms performed with a water-soluble contrast medium. The interval between insult and diagnosis was 1 day (26 hours) to 25 days. All patients were transferred from other hospitals and had fever and empyema.

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Table 1. Summary of Clinical Data

Patient No.	Age (y)	Sex	Time to Diagnosis[a] (d)	Location[b]	Cause
1	58	M	1	Lower third	Boerhaave's syndrome
2	16	M	5	Upper third	Blunt chest trauma
3	60	F	6	Lower third	Foreign body
4	47	M	2	Upper third	Foreign body
5	26	M	2	Upper third	Blunt chest trauma
6	73	F	6	Middle third	Foreign body
7	50	M	25	Upper third	Penetrating injury

[a] This is the interval between insult and diagnosis. [b] This is the site of perforation on the thoracic esophagus.

In 4 patients, the location of the perforation was in the upper third of the thoracic esophagus; in 1 patient, the middle third; and in 2 patients, the lower third of the thoracic esophagus (see Table 1). The perforation was caused by a foreign body in 3 patients (fish bone in 2 and chicken bone in 1), trauma in 3, and Boerhaave's syndrome caused by gastric cancer with pyloric obstruction in 1.

Surgical Treatment

All patients were operated on soon after the diagnosis was made. At operation, the perforation was debrided and closed directly through a posterolateral thoracotomy in all patients. We could always close the mucosal layer. No local flap was used to reinforce the perforation. Decortication with wide mediastinal and pleural drainage was performed. One of the pleural tubes was placed near the perforation and was fixed with absorbable sutures. The incisional wound of the thoracotomy was left open and wet packed after closure of the muscular layer of the chest wall. Patients were then put in the supine position.

An absorbable ligature was placed at the esophagogastric junction deep to the vagus nerve through an upper median laparotomy. A feeding gastrostomy was inserted for nutritional supply. The cervical esophagus was then isolated. A T tube was introduced through an esophagotomy for drainage of saliva. Another absorbable ligature was placed on the cervical esophagus distal to the T-tube esophagostomy (Fig 1). In this way, total esophageal exclusion was established. Additional therapy included correction of acid-base and electrolyte imbalance, antibiotics according to the culture results, and nutritional support through the gastrostomy. Continuity of the esophagus was established after spontaneous absorption of the ligatures and by removal of the T tube approximately 4 weeks after the initial operation. Oral intake was then initiated.

Subtotal gastrectomy with gastrojejunostomy was performed 1 week after the first operation on a patient with pyloric obstruction caused by gastric cancer initially presenting as Boerhaave's syndrome (patient 1). Cancer cell infiltration to the celiac lymph nodes was demonstrated on pathological specimens. Latissimus dorsi muscle flap translocation was done in 1 patient (patient 7) 4 weeks after total esophageal exclusion when complete healing of the perforated esophagus was demonstrated. This patient had a big defect on the back, and necrotizing fasciitis developed because of delayed treatment of the penetrating injury.

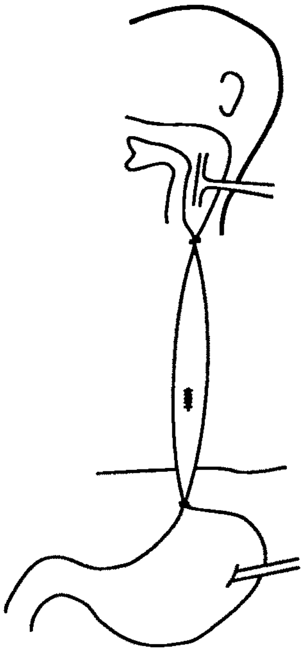

Fig 1. *Esophageal exclusion.*

Results

All 7 patients survived. Four recovered uneventfully. Two had localized incisional wound infections and were treated conservatively. One patient experienced repeated bleeding from the left carotid artery because of erosion from the T tube. After primary repair of the carotid artery, the bleeding stopped. Two patients who had hepatic and renal failure because of sepsis also recovered.

Four weeks after operation, the T tube was removed and endoscopic examination of the esophagus was performed. It showed a well-healed esophagus in every patient. The endoscope could easily push open or pass through previously ligated segments of the esophagus and reach the stomach. Esophagography, performed with a water-soluble contrast medium in all patients after healing of the esophagostomy wound, showed no leakage or stenosis of the esophagus. No secondary thoracotomy or esophageal reconstruction was necessary.

All patients enjoyed normal swallowing during follow-up (range, 12 to 50 months; mean follow-up, 23 months). No patient complained of dysphagia. One patient (patient 1) died of metastatic cancer 15 months after the esophageal perforation. Two patients (patients 2 and 3) were lost to follow-up 29 and 50 months after the esophageal perforation.

Comment

Perforation of the esophagus is often fatal unless promptly diagnosed and effectively treated within 24 hours. This is well demonstrated by the sharp rise in mortality rates when treatment is delayed [1–7]. However, because this disease is not common and has a variety of symptoms, none of which are diagnostic, there is often a delay in diagnosis. Recognizing that frequent failure of surgical closure of the perforation was the principal problem, surgeons have tried a wide range of different approaches. Some surgeons [5, 6, 11] considered attempts to close the perforation hopeless and recommended simple drainage or T-tube drainage of the esophagus, but this was consistently associated with a high rate of mortality. Loop and Groves [12] recommended early thoracotomy and closure of the perforation even in patients who were a poor surgical risk. Fistulas developed in 39% of 158 patients treated by primary repair [1, 2, 4–6, 11, 13–16]. The frequency of leakage for repairs done after 24 hours was at least 50% [1, 2, 14].

The frequent failure of delayed closure led to a variety of attempts to buttress the suture line with autogeneous tissue flap [13, 17, 18]. However, they are not uniformly successful in preventing leakage [19]. In recent years, muscle flaps have been used with increasing frequency, but they should be placed only very early for trauma and when the esophagus cannot be closed primarily [19].

A few groups have used esophagectomy in advanced cases to correct intrinsic esophageal pathology or to control a complex fistula. Six reports with 23 patients had an overall mortality rate of 26% [2–4, 7, 8, 13]. Johnson and associates [20] suggested that primary esophagogastrectomy should be performed within a few hours after perforation because, with greater delay and the presence of more severe infection, the resection would be made in badly contaminated tissue with potential risks to the esophageal anastomosis. For delayed cases, they [8] recommended exclusion of the thoracic esophagus.

The principle of exclusion and diversion has long been applied to the treatment of fistula of the intestinal tract. Different methods of esophageal diversion have been suggested that are somewhat analogous to the use of a colostomy for injury of the distal colon. Johnson and colleagues [8] proposed dividing the stomach at its junction with the esophagus. The cervical esophagus is also diverted in continuity by opening it longitudinally and suturing its muscularis to the subcutaneous fascia and skin.

The most common method is that reported by Urschel and co-workers [9] in 1974. They performed esophageal exclusion by ligating the esophagus distal to the perforation with an umbilical tape or Teflon felt deep to the vagus nerve to prevent gastroesophageal reflux and by proximal cervical esophagostomy to prevent salivary contamination. The experience of Dr Urschel [21] comprises 58 patients. Forty-nine had delayed diagnosis or treatment, and only 5 died with this procedure. Nesbitt and Sawyers [14] reported in 1987 that eight of nine diversion procedures were successful.

The principles involved are to close all the perforations and prevent further contamination of the suture line from gastroesophageal reflux and saliva. These radical approaches provide good results, especially when the initial operation has been delayed or has been unsuccessful. However, they do present the disadvantages of prolonged discomfort and multiple operations for esophageal reconstruction. Popovsky [10] used a double strand of absorbable Dexon to ligate the distal esophagus, making a second thoracotomy for removal of the ligature unnecessary. Using this modified method, however, a second operation to close the cervical esophagostomy is still necessary. Besides, his method was side-to-side and does not provide 100% diversion.

In our series, we used Dexon ligatures to occlude the esophagus at the esophagogastric junction and the cervical esophagus distal to the T tube esophagostomy in 7 patients. This technique provides complete diversion of saliva through the T-tube cervical esophagostomy and prevents reflux of gastric contents to the esophagus. The attractive concept of this method for esophageal exclusion is that the Dexon ligatures dissolve within 3 to 4 weeks, and an endoscope can be easily passed to open the esophagus. Secondary procedures to reestablish esophageal continuity are not necessary. With this technique, we did not have to resect any part of the esophagus, regardless of how bad the perforation looked. Our experience indicates that esophageal perforation can be closed by primary suture after debridement. As all 7 patients had repair more than 24 hours after perforation, the longest time being 25 days later, there may be no fixed period beyond which primary debridement and repair cannot be done.

All our patients survived. The immediate cause of death after esophageal perforation is usually sepsis. Necrotizing mediastinitis develops with impressive rapidity. Radical decortication and wide mediastinal and pleural drainage are important to eradicate the infection source. However, prevention of leakage around the suture line is also important, no matter how small the leakage, as it adds another source of sepsis for an already sick patient. Total esophageal exclusion by our method allows the perforated segment of esophagus an interval to heal while excluded from the flow and contamination of gastrointestinal contents and saliva. It also gives the patient a chance to recover from sepsis and organ failure without further insults from leakage. We do not recommend using this method to repair the perforated esophagus with distal stricture, benign or malignant. These lesions should be bypassed or resected.

In conclusion, we present our experience with 7 patients who had delayed diagnosis of thoracic esophageal perforation. Primary repair of the perforation and total exclusion of the esophagus using absorbable ligatures plus T-tube cervical esophagostomy make a one-stage operation possible and safe. We believe that surgical repair is indicated regardless of the delay in diagnosis and that primary closure of the perforation after debridement with total esophageal exclusion provides the best chance for recovery.

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Operation for Cavitating Invasive Pulmonary Aspergillosis in Immunocompromised Patients

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Invasive pulmonary aspergillosis is a specific form of pulmonary *Aspergillus* infection that occurs almost exclusively in immunocompromised patients. It differs both histologically and in its clinical course from classic aspergillomas. During a 5-year period (1986–1990), 8 patients underwent resection for cavitating invasive pulmonary aspergillosis that developed as a consequence of neutropenia during chemotherapy for malignancy. There were no perioperative deaths and no complications. This contrasts with reports of operation for classic aspergillomas. Histologic examination of the resected specimens showed that cavitating invasive pulmonary aspergillosis differed from classic aspergillomas. They consisted of necrotic lung tissue invaded by fungus with separation from the surrounding lung so that the sequestrum had the appearance of a fungus ball. Pulmonary aspergillosis is a common complication of profound neutropenia. The first hemoptysis in this group of patients is often life-threatening. The excellent results of operation in our series of patients may be attributed to their young age, good pulmonary function, and limited operation. This has lead us to recommend early surgical intervention in invasive aspergillosis once cavitation develops.

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Pulmonary infection with the *Aspergillus* fungus may take one of three forms: first, bronchopulmonary aspergillosis, an allergic condition; second, classic aspergillomas, which arise when the fungus proliferates in a preexisting cavity; and third, invasive pulmonary aspergillosis, which occurs almost exclusively in the immunocompromised patient [1, 2]. With the widespread use of intensive chemotherapy, invasive pulmonary aspergillosis is increasingly recognized, occurring in up to 20% of patients undergoing treatment for acute leukemia [3]. In these patients, *Aspergillus* infection gives rise to a fungal pneumonia, which progresses to pulmonary infarction in approximately 30% of patients [1, 4, 5]. The infarcted pieces of lung may then undergo cavitation. Cavitating invasive aspergillosis resembles classic aspergillomas on chest roentgenograms, with an air crescent sign present [6]. However, the pathogenesis and natural history of these lesions are very different with important implications for management. Once cavitation develops in invasive pulmonary aspergillosis there is a risk of massive hemoptysis, and operation is advocated [7, 8].

In a review of the world literature in 1988, Kibbler and associates [7] identified 38 cases of cavitating invasive pulmonary aspergillosis [4, 5, 9, 10]. Of the 32 patients for whom details are given, 9 underwent operation, 6 died of massive hemoptysis, and 17 had minor or no hemoptysis. Kibbler and associates consequently recommended "surgical intervention when possible . . . as soon as possible after the diagnosis" [7]. We present a series of eight consecutive resections for cavitating invasive pulmonary aspergillosis and contrast these cases with classic aspergillomas.

Patients and Methods

Between 1985 and 1990, cavitating invasive aspergillosis developed in 10 patients as a result of intensive chemotherapy for malignancy. Two patients died of massive hemoptysis before being considered for operation. After this all patients with invasive pulmonary aspergillosis in whom cavitation developed underwent pulmonary resection when the cavitation developed.

Eight patients were operated on over a 5-year period. The age ranged from 18 to 63 years (mean, 42 years), and there were 4 men and 4 women. Five patients had acute leukemia (acute myeloid leukemia, 1; acute lymphoblastic leukemia, 4), 2 patients had lymphomas (pulmonary, gastric), and 1 patient had a plasmacytoma. Four patients had had bone marrow transplants (Table 1). Fungal pneumonia developed in all 8 patients while they were neutropenic (white blood cell count, $<1 \times 10^9/L$ [$< 1,000/\mu L$]) as a result of chemotherapy.

The diagnosis of fungal pneumonia was based on clinical features, failure to respond to antibiotic therapy, and retrieval of fungi by bronchoscopic washings [11]. Bronchoscopy yielded *Aspergillus* in 5 patients, rhizopus in 1, and was negative in 2 patients. In both patients with negative bronchoscopy, histologic examination of the resected specimen confirmed *Aspergillus* infection. *Rhizopus* is a genus in the family Mucoraceae related to *Aspergillus* that may cause fungal pneumonia and progress to cavitation [12]. Serologic examination was not routinely

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Table 1. Patient Details

Patient No.	Age (y)	Sex	Underlying Disease	Resection	Bronchoscopy Yielded
1	45	M	Plasmacytoma	RUL	Negative
2	18	M	ALL (BMT)	RUL	*Rhizopus*
3	20	F	ALL (BMT)	Segmentectomy ×3: apical LLL, anterior LUL, posterior LLL	*Aspergillus*
4	43	F	Gastric lymphoma	LUL	*Aspergillus*
5	63	M	AML (BMT)	RUL	*Aspergillus*
6	41	F	ALL (BMT)	LUL	*Aspergillus*
7	47	F	Pulmonary lymphoma	RLL	Negative
8	56	M	AML	LUL	*Aspergillus*

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BMT = bone marrow transplant; LLL = left lower lobectomy; LUL = left upper lobectomy; RLL = right lower lobectomy; RUL = right upper lobectomy.

used in our series as negative results do not exclude the diagnosis. All patients received intravenous amphotericin preoperatively and postoperatively.

Results

Seven lobectomies and one multiple segmental resection were performed. The lesions were sited in the periphery of the lung in all cases. In all 8 patients the blood counts had returned to normal before operation. However, 1 patient required perioperative platelet support for a qualitative bleeding defect. Preoperative pulmonary function test showed a mean forced expiratory volume in 1 second/forced vital capacity of 2.01/2.70. In general, the maximum amount of normal lung was preserved.

In patients who were operated on early after the development of cavitation, the operations were less technically difficult. The pleural surface was easily dissected from the chest wall. Patients in whom there had been a delay in referral for operation were much more difficult candidates. The lung was densely adherent to the chest wall and, in several patients, the chest wall formed part of the wall of the cavity. Despite this there were no postoperative complications. In particular there were no cases of postoperative bleeding, empyema, or residual space problems. This contrasts strongly with patients who have operation for classic aspergillomas [13–16]. In a large series of patients having resections for aspergillomas, postoperative bleeding occurred in 18%, empyema in 36%, and bronchopleural fistula in 21%. In addition, 9 of 53 patients required pneumonectomy [16].

Comment

Invasive pulmonary aspergillosis is a condition occurring almost exclusively in the immunocompromised patient. The fungus behaves as an opportunistic infection giving rise to a fungal pneumonia. Subsequent invasion of large blood vessels by the fungus leads to pulmonary infarction. Lysis of this infarct by phagocytes leads to separation of this infarcted piece of tissue from the surrounding lung. Chest roentgenographic appearance resembles that of classic aspergilloma, with an air crescent sign (Fig 1). However, this lesion contrasts strongly with classic aspergilloma. Classic aspergilloma develops when a fungus colonizes and proliferates in a preexisting cavity. The lesion in invasive pulmonary aspergillosis is best termed a mycotic lung sequestrum [7], as it consists of a necrotic piece of lung, invaded by fungus, that has separated from the surrounding lung (Fig 2).

The natural history of cavitating invasive aspergillosis is also very different from that of classic aspergillomas. Hemoptysis in classic aspergillomas occurs in 50% of patients and is severe or recurrent in only 10% [17, 18].

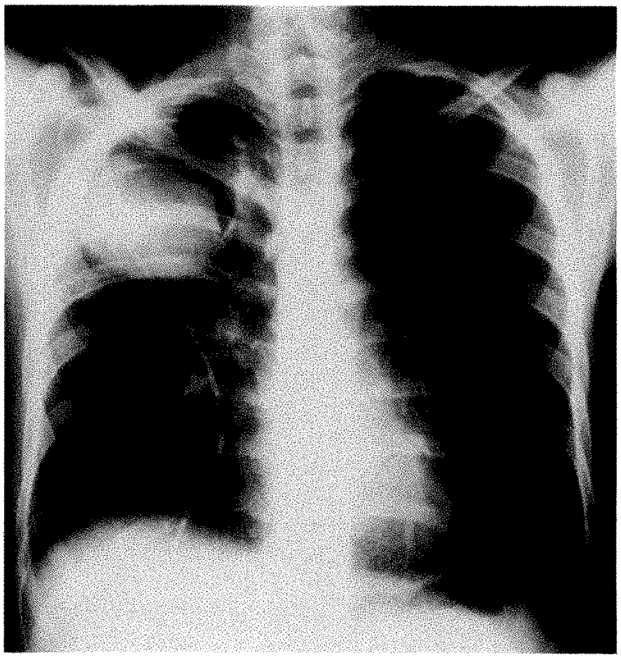

Fig 1. (Patient 2.) Chest roentgenogram showing a cavity in the right upper lobe containing a mycotic lung sequestrum. An air crescent sign is seen. A Hickmann catheter is in situ.

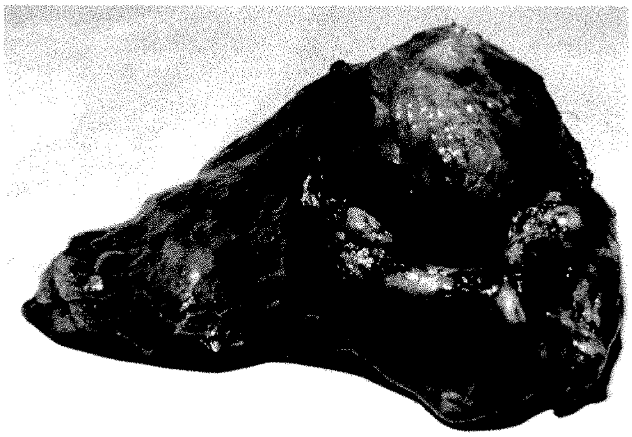

Fig 2. (Patient 2.) Right upper lobectomy specimen showing mycotic lung sequestrum separated by a plane of cleavage from the surrounding lung.

Bleeding classically occurs from bronchial arteries and usually stops spontaneously [18, 19]. Hemoptysis in cavitating invasive aspergillosis is usually massive, and the first hemoptysis is often fatal [4, 7]. The reason for this is unclear. However, we postulate that bleeding in these cases may be from intercostal arteries. In invasive pulmonary aspergillosis the pulmonary infarct extends to the periphery of the lung and lies up against the chest all, to which it adheres. Subsequent lysis of the infarct leads to separation of the mycotic lung sequestrum. We postulate that extension of this process to the adjacent chest wall may lead to erosion of intercostal arteries. Bleeding from such large arteries is unlikely to stop spontaneously, and we suggest that this may be the reason why the first hemoptysis in this group of patients is often fatal.

The results of operation in this group of patients with cavitating invasive pulmonary aspergillosis contrasts strongly with those of operation for classic aspergillomas. This reflects the differences in the pathogenesis of the two conditions. Patients with classic aspergillomas have preexisting lung pathology, most commonly tuberculous, with extensive damage throughout the lung. This leads to several technical problems not present in invasive pulmonary aspergillosis [20]: first, induration of the hilar structures by tuberculosis; second, poor expansion of the remaining lung leading to residual space problems; and third, compromised pulmonary function and poor respiratory reserve.

This contrasts with invasive pulmonary aspergillosis, in which the hilar structures are preserved, the residual lung is uninvolved and expands well and, because of the localized nature of the disease, limited resection is possible and pulmonary function is good. In addition, the average age in our group of patients is younger, reflecting the underlying disease entities.

Contrary to what might be expected, low platelet counts or white blood cell counts have not proved a problem in our patients. As in previous reports, cavitation of the pulmonary infarct appeared as the patient recovered from neutropenia. It has been postulated that cavitation requires the action of phagocyte-derived proteolytic enzymes [21, 22].

In conclusion, despite the similarities on chest roentgenograms between classic mycetomas and cavitating invasive pulmonary aspergillosis, there are many differences in pathogenesis and natural history with implications for management. We advocate resection in cavitating invasive aspergillosis as soon as the lesion becomes apparent for two reasons: first, delay may result in life-threatening hemoptysis; and second, we have found that with time these lesions become more adherent to the chest wall and more difficult to resect.

Furthermore, many of these patients will be subjected to further cycles of chemotherapy with consequent pancytopenia. Neutropenia may allow the *Aspergillus* fungus to disseminate throughout the lung, and any hemoptysis in a patient with a low platelet count is likely to be fatal. Finally, in contrast to the results of operation in patients with classic aspergillomas, the operative results in patients with invasive pulmonary aspergillosis would appear to be excellent, as shown by our series of patients who had no serious postoperative complications.

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Reinfusion of Shed Blood After Coronary Operation Causes Elevation of Cardiac Enzyme Levels

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We studied the effect of reinfusing mediastinal and chest tube drainage (autotransfusion) after coronary artery bypass grafting on circulating levels of creatine kinase, lactate dehydrogenase, and serum glutamic-oxaloacetic transaminase in 20 patients. Reinfusion of 469 ± 171 mL (mean ± standard deviation) of drainage caused enzyme levels to rise to 372% (creatine kinase), 159% (serum glutamic-oxaloacetic transaminase), and 143% (lactate dehydrogenase) of their levels before autotransfusion. The MB fraction of the circulating creatine kinase was not elevated. Enzyme changes caused by autotransfusion can potentially mimic or mask the presence of perioperative myocardial infarction. Enzyme determinations after coronary artery bypass grafting must be carefully interpreted when reinfusion of shed blood is used as a blood salvage technique. Routine measurement of these enzymes after operation may not be warranted.

(Ann Thorac Surg 1992;53:625–7)

Cardiac surgery programs consume enormous quantities of blood products. Although hepatitis and transfusion reactions are the most important medical problems associated with transfusion, the fear of human immunodeficiency virus transmission has made many patients wary of receiving homologous blood. Changes in surgical technique and postoperative management have reduced the per-case need for transfusion in the past 10 years. Reinfusion of postoperative chest and mediastinal drainage (autotransfusion) is one method that has been used to minimize the blood requirements after coronary artery bypass grafting [1–3]. There have been no adverse affects associated with this procedure.

After beginning routine autotransfusion in our postoperative cardiac patients, we noted an increase in the frequency of elevations of creatine kinase (CK), lactate dehydrogenase (LDH), and serum glutamic-oxaloacetic transaminase (SGOT) levels despite the absence of electrocardiographic evidence of myocardial injury. This study was performed to determine whether autotransfusion could account for the observed changes in cardiac enzymes.

Material and Methods

The plasma levels of CK, CK-MB, LDH, and SGOT were measured in the plasma and shed blood of 20 patients after nonemergent coronary bypass grafting. Creatine kinase, LDH, and SGOT levels were measured spectrophotometrically (American Monitor, Parallel analyzer), and the percent MB fraction of the CK was determined electrophoretically. The chest and mediastinal tube drainage was collected in a reinfusion system (Pleur-evac; Deknatal, Fall River, MA) stabilized with 30 mL of citrate-phosphate-dextrose solution under a constant suction of 20 cm H_2O. Four hours after admission to the surgical intensive care unit, the collected drainage was reinfused without washing or centrifugation through a standard 20-μm blood filter (Pall Blood Transfusion filter, No. SQ40S; Pall Biomedical Inc, Fajardo, Puerto Rico). Blood was collected from an indwelling arterial line at admission to the surgical intensive care unit, immediately before and after autotransfusion, and 24 hours after admission to the surgical intensive care unit. Patients were excluded if there was electrocardiographic or clinical evidence of myocardial injury. In 4 control patients the shed blood was collected and analyzed but not reinfused.

All patients had saphenous vein aortocoronary grafts placed through a median sternotomy approach. Seventeen of the 20 had left internal mammary artery grafts placed to the left anterior descending coronary artery. Intraoperative protection included total body hypothermia to 28°C, topical saline slush, cold potassium cardioplegia, and cardiopulmonary bypass with a membrane oxygenator (Cobe Laboratories, Lakewood, CO). Intraoperative blood removed by suction from the operative field was reinfused through the bypass circuit in all patients. All patients were extubated and free of inotropic or vasoactive infusions 16 hours or less after operation.

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Table 1. Study Population[a]

Variable	Autotransfused (n = 16)	Controls (n = 4)	p Value
Age (y)	62.1 ± 9.7	66.5 ± 10.2	NS
M/F	15/1	2/2	NS
No. of vein grafts	3.8 ± 0.6	3.5 ± 1.0	NS
LIMA	14/16	3/4	NS
Volume of shed blood (mL)	469 ± 171	435 ± 145	NS

[a] Age, no. of vein grafts, and volume are expressed as mean ± standard deviation.

LIMA = left internal mammary artery graft; NS = not significant.

Data were analyzed using a two-tailed Student's t test, and differences were considered significant at probabilities of less than 5%.

Results

The age, sex, operation, and volume of drainage in the autotransfused and control patients were similar (Table 1).

The CK, LDH, and SGOT levels were markedly elevated in the shed blood of all patients and controls (Table 2). The percent MB band of the CK in the shed blood was the same as that of the admission circulating blood.

The circulating levels of LDH, SGOT, and CK were significantly increased after reinfusion of shed blood when compared with levels in control patients or pretransfusion levels (Fig 1). The largest change occurred in the CK level, which increased from a mean of 272 IU to 941 IU after autotransfusion. The percent MB of the CK in the circulating blood was not affected by autotransfusion.

Twenty-four hours after autotransfusion, the CK (784 versus 197 IU; $p < 0.001$), LDH (392 versus 235 IU; $p < 0.05$) and SGOT (114 versus 56 IU; $p < 0.05$) levels were still significantly elevated when compared with those of the control patients.

Comment

In 1819, Blundell discussed the use of patients' blood losses as a source for intravascular replacement. In 1978, Schaff and associates [1] first described the autotransfusion of postoperative shed blood after coronary artery bypass grafting. They and others have extensively reviewed the hematologic and coagulation properties of shed mediastinal blood [1, 4].

In 1981, Cordell and Lavender [5] measured SGOT and LDH levels in 114 patients before and after cardiac operations with and without intraoperative reinfusion of blood losses. They did not reinfuse postoperative blood losses. Although not statistically significant, there appeared to be an increase in the level of LDH after intraoperative reinfusion of operative blood losses. We can find no previous description of cardiac enzyme concentrations in postsurgical pleuropericardial shed blood, or the effects of reinfusion of postoperative shed blood on circulating levels of enzymes. In a recent review of blood conservation techniques used in cardiac operations, no comment was made about CK, LDH, or SGOT levels in postoperative shed blood or intraoperative collections [6].

Pleuromediastinal drainage after coronary artery bypass grafting contains very high concentrations of CK, LDH, and SGOT. Autotransfusion of shed blood causes an immediate rise in the circulating levels of these enzymes. The changes in circulating enzyme levels seen after autotransfusion are about those expected from the simple mixing of the shed blood in the 5-L intravascular space.

We did not perform nuclear or echocardiographic studies to more completely rule out the presence of small myocardial infarctions. However, none of the patients had electrocardiographic changes, elevation of pulmonary capillary wedge pressure, or a reduced cardiac output, and all 20 patients had rapid postoperative recoveries. The control patients showed no changes in circulating enzyme levels during the same postoperative period.

Our control group comprised 4 patients. The volume of the shed blood and its enzyme concentrations were the same in the 4 control patients as in the 16 autotransfused patients. Despite the small control group, the difference in circulating levels of CK between autotransfused and control groups was highly significant as analyzed by Student's t test. There was no overlap in CK level among the two groups. The 4 control patients' circulating CK levels ranged from 102 to 267 mU/mL at the same time after operation that the autotransfused group had circulating levels of CK ranging from 336 to 2,485 mU/mL. Confirmation of our observations on larger numbers of patients would be desirable, but not likely to change the conclusion.

Although we did not specifically identify the source of the enzymes, it is likely that the pleuromediastinal/mediastinal drainage is a combination of blood and fluid released from chest wall muscle and stroma, with only a small amount of extravasation from tissue with a high percentage of the MB fraction of CK such as ventricle, atrium, or aorta. In 1985, Graeber and associates [7] showed that skeletal muscle of canine chest wall has a high total CK level (626 to 770 IU/g tissue), with 4.6% to 9.0% of this being CK-MB. There is no evidence that the mediastinal or pleural spaces can concentrate enzymes from the circulating blood, so bleeding alone cannot account for the observed changes.

The total CK, CK-MB, LDH, and SGOT levels have all

Table 2. Enzyme Levels of Shed Blood[a]

Enzyme	Autotransfused	Controls	p Value
CK (mU/mL)	6,298 ± 4,023	6,464 ± 6,289	NS
CK-MB (%)	6.2 ± 4.2	5.0 ± 0.8	NS
SGOT (mU/mL)	303 ± 89	302 ± 232	NS
LDH (mU/mL)	1,343 ± 269	1,223 ± 785	NS

[a] All data are expressed as mean ± standard deviation.

CK = creatine kinase; LDH = lactate dehydrogenase; NS = not significant; SGOT = serum glutamic-oxaloacetic transaminase.

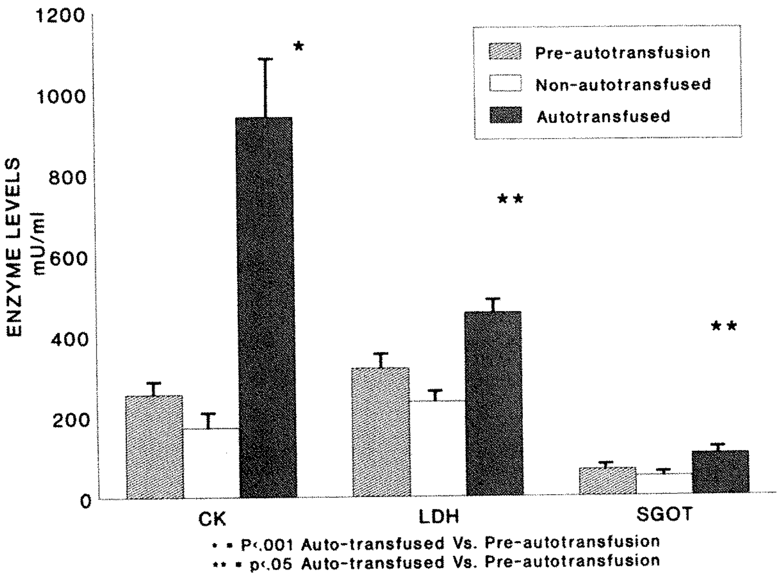

Fig 1. Circulating enzyme levels (International Units, mean ± standard error of the mean) before and 1 hour after scheduled reinfusion in the autotransfused and nonautotransfused control groups. Values of p *represent comparison of autotransfused patients with nontransfused controls. (CK = creatine kinase; LDH = lactate dehydrogenase; SGOT = serum glutamic-oxaloacetic transaminase.)*

been used to help detect the presence of myocardial injury after coronary artery bypass grafting. Baur and coworkers [8] showed that total CK-MB release integrated over the first 48 hours after operation and peak CK-MB both were able to discriminate patients with perioperative myocardial infarctions from those without myocardial injury. They did not reinfuse shed blood.

We believe that autotransfusion of pleuromediastinal drainage can confuse enzymatic detection of perioperative myocardial infarction in two ways. First, the increased enzyme levels may suggest the presence of myocardial damage, although the lack of CK-MB elevation or electrocardiographic changes in the setting of normal hemodynamics should help to rule out large infarctions. Perhaps more importantly, the increase in total CK (the denominator in the percent MB calculation) may lower the percent MB fraction associated with a small perioperative infarction, and potentially important interventions (ie, extended continuous electrocardiographic monitoring) may be withheld. At best, a redefinition of the normal range for these enzymes may be required to continue to use them as an important aid in the detection of cardiac injury in the autotransfused patient. The wide variance in observed levels significantly limits their sensitivity and specificity. We believe that the cost of routinely measuring these enzymes is probably not warranted.

In conclusion, we have shown that the shed blood after coronary artery bypass grafting has very high concentrations of CK, LDH, and SGOT. Reinfusion of this blood results in immediate increases in the levels of all three enzymes, which persist for 24 hours. These enzyme elevations may mimic the presence of cardiac injury and may also mask the occurrence of small myocardial infarctions. In programs using reinfusion techniques, routine postoperative enzyme levels are of limited value and should be cautiously interpreted if they are measured at all.

We thank the staff of the surgical intensive care unit for their help in the collection of data.

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Initial Experience With Low-Potassium Cold Blood Cardioplegia: A Clinical Comparative Study

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This study presents the results of bypass grafting in 96 patients operated on for triple-vessel coronary artery disease between May 1988 and September 1990. In the first 54 patients a cold crystalloid solution was employed, and in the 42 more recent patients cold blood low-potassium cardioplegia was employed. There were no differences in postoperative cardiac index or left ventricular stroke work index. Yet, in patients with impaired prebypass left ventricular stroke work index, postbypass left ventricular performance correlated negatively with duration of aortic cross-clamping in the cold crystalloid group ($r = -0.441$, $p = 0.045$). In contrast, no correlation was found in the cold blood low-potassium group ($r = 0.125$, $p = 0.587$). The incidence of myocardial infarction, need for inotropic support, and need for intraaortic balloon counterpulsation were similar among the groups. Release of the myocardial isoenzyme creatine kinase-MB from 12 to 30 hours after operation was significantly less in the low-potassium blood cardioplegia group. The use of low-potassium blood cardioplegia resulted in a marked reduction in the operative administration of fluids (1,527 ± 87 versus 3,511 ± 148 mL; $p < 0.001$). In conclusion, low-potassium cold blood cardioplegia is a simple and effective method of myocardial protection. The fact that left ventricular stroke work index recovery was not dependent on the duration of aortic occlusion and that release of the MB isoenzyme of creatine kinase was reduced in the low-potassium blood cardioplegia group implies better myocardial protection.

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Clinical studies comparing sanguineous and asanguineous cardioplegic solutions demonstrated by prospective trials that blood cardioplegia (BCP) provides superior protection for the left ventricle in elective coronary artery bypass grafting [1, 2], reduces the risk of urgent revascularization for unstable angina [3], and influences perioperative but not late postoperative function after elective coronary artery bypass grafting [4]. Yet, BCP has not gained wide acceptance in clinical practice. Reasons for this lack of popularity could be the apparent controversy about questions such as the ideal conditions of administration of BCP (temperature and hematocrit) and the belief that BCP is more difficult to handle than crystalloid cardioplegia (CCP) and must be restricted to high-risk patients. This report presents data on the clinical application of BCP using a technique of administration at low temperature and low potassium concentration, very similar to a routine technique of CCP.

Patients and Methods

This study comprises 96 patients operated on for triple-vessel coronary artery disease between May 20, 1988, and September 10, 1990. All the operations were performed by one surgeon working with the same anesthetic team, with identical techniques. Thus, aside from the type of cardioplegic solution used, all operations were conducted in the same manner. We contrasted our observations made in the first 42 consecutive patients in whom we used cold blood low-potassium cardioplegia with those obtained in the 54 previous consecutive patients in whom the crystalloid solution routinely used in our hospital was administered. The two series did not overlap.

To compare similar techniques of administration of the cardioplegic solution through the ascending aorta and through the bypass grafts, we excluded complex coronary revascularizations using bilateral or sequential mammary artery grafts, redo operations, and coronary revascularization associated with valvular replacement. During the study period, the frequency of high-risk patients increased. Therefore, the two groups of patients showed significant differences with respect to New York Heart Association functional class and sex ratio (Table 1). However, major coronary artery stenoses defined as luminal diameter stenosis of 50% or more of the left main trunk and 60% or more of other arteries did not differ significantly among the groups. Likewise, preoperative left and right ventricular ejection fraction (angiographic and isotopic) were similar. The presence of cold agglutinins at a titer exceeding 1/16 (dilutions of 1/32, 1/64, and more) at 4°C was considered a contraindication to the use of cold

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Table 1. Clinical Characteristics

Variable	Blood	Crystalloid	p Value
Preoperative			
Patients (n)	42	54	
Age (y)	63.7 ± 1.44	64.9 ± 1.05	0.480
Age range (y)	38–86	37–82	
Sex (M/F)	27/15	46/8	0.017
BSA (m^2)	1.80	1.87	0.049
NYHA (II/III/IV)	11/10/21	24/21/9	0.002
Diseased vessels (%)			
Left main trunk	16.7	33.3	0.065
LAD	92.9	79.6	0.069
Diagonal	42.9	35.2	0.444
Circumflex	61.9	50.0	0.245
Marginal 1	42.9	51.9	0.382
Marginal 2	23.8	20.4	0.686
Right coronary	92.9	88.9	0.508
LV EF angio	63.8 ± 2.3	58.9 ± 2.7	0.174
LV EF isot	48.1 ± 2.7	48.3 ± 2.7	0.975
RV EF isot	42.3 ± 2.4	43.7 ± 1.5	0.593
Perioperative			
Distal anastomoses (3/4/5)	29/13/0	37/16/1	0.673
Use of LIMA	92.9%	96.3%	0.382
Cross-clamp time (min)	84.0 ± 2.6	84.7 ± 2.2	0.831
Pump time (min)	141.1 ± 3.7	145.6 ± 3.8	0.413
Pump assist (min)	57.1 ± 2.8	60.9 ± 2.6	0.326
Pulsatile flow (%)	87.8	92.6	0.224
IABP (%)	4.8	3.7	0.780

angio = determined by contrast angiography; BSA = body surface area; EF = ejection fraction; IABP = intraaortic balloon pulsation; isot = determined by isotopic ventriculography; LAD = left anterior descending artery; LIMA = left internal mammary artery; LV = left ventricular; NYHA = New York Heart Association functional class; RV = right ventricular.

blood cardioplegia, and this was the case in 11.9% of the patients.

A peripheral and an arterial line were placed under local anesthesia. General anesthesia was performed with fentanyl citrate (25 μg/kg) and pancuronium bromide (Pavulon; Organon Inc, West Orange, NJ) (0.1 mg/kg), and all the patients were kept on the respirator until the next morning. A Swan-Ganz thermodilution catheter was introduced percutaneously through the internal jugular vein. Cardiac output was measured with thermodilution technique, using a cardiac output computer (Hellige GmbH, Freiburg im Breisgau, Germany). The results were stated as the mean of three consecutive recordings. Donor blood, plasma, and electrolyte solutions were infused during and after the operation to maintain the preoperative wedge and mean pulmonary artery pressures.

Standard cannulation of the ascending aorta was performed. The ascending aorta was vented through a catheter having a Y connection to the cardioplegic line. Cardiac drainage was realized through the atrial appendage using a USCI No. 34 two-stage cavoatrial catheter. The extracorporeal circulation was performed with a Stöckert heart-lung machine allowing pulsatile flow, using an SMO Sarns (Sarns 3M Health Care, Ann Arbor, MI) or Maxima Medtronic (Medtronic Inc, Anaheim, CA) membrane oxygenator with a closed system of perfusion. The ascending aorta was cross-clamped. Moderate hemodilution (hematocrit, 0.25 to 0.30) and systemic hypothermia (25°C) were maintained during aortic occlusion.

When CCP was used, 1,000 mL of the solution was infused initially with a pressure bag through the aortic root. The composition and characteristics of administration of each cardioplegic solution obtained from 10 patients are listed in Table 2. Cardioplegic fluid (300 to 500 mL) was reinfused after each distal anastomosis into the aortic root and through each completed saphenous vein graft. Because the time to achieve complete electrical arrest is longer with sanguineous solutions and the priming of the BCP heat exchanger system takes 1 minute from aortic cross-clamping, the following two-step approach was used in the BCP group. Rapid initial arrest was obtained by instillation of 500 mL of CCP solution while the BCP system was primed. The BCP solution was then infused through a roller pump into the aortic root at a flow of 250 mL/min over 2 minutes. The cardioplegic delivery system consisted of disposable tubing to deliver a 4:1 blood/crystalloid cardioplegic ratio (HE 100 heat exchanger; American Bentley Hospital Supply Corp, Irvine, CA). The tubing was attached to a coronary cardioplegic adapter containing four limbs that allows simultaneous cardioplegic distribution into the aorta and into the vein grafts (CDS-004; Research Medical, Inc, Salt Lake City, UT). Reinfusion into the vein grafts and the aortic root

Table 2. Cardioplegic Solutions

Variable	Blood	Crystalloid
Composition		
Na (mEq/L)	138.9 ± 0.9	133
K (mEq/L)	8.5 ± 0.5	16
Mg (mEq/L)	5.4 ± 0.9	. . .
Ca (mEq/L)	7.0 ± 0.2	7
Cl (mEq/L)	110.3 ± 1.0	118
P (mEq/L)	1.3 ± 0.1	0.1
HCO_3 (mEq/L)	19.3 ± 0.3	5.5
Osmolarity (mOsm/L)	305.2 ± 2.0	289
pH	7.34 ± 0.01	7.4
Hemoglobin (g/100 mL)	6.1 ± 0.4	. . .
Hematocrit	0.17 ± 0.01	. . .
PO_2 (mm Hg)	248.3 ± 31.6	. . .
PCO_2 (mm Hg)	33.1 ± 1.0	. . .
Conditions of administration		
Proximal injection pressure (mm Hg)	183.5 ± 8.8	. . .
Aortic root pressure (mm Hg)	64.3 ± 5.5	66.2 ± 5.7
Temperature of perfusate (°C)	8.0 ± 0.3	4
Temperature of septum (°C)	11.1 ± 0.7	11.7 ± 0.9

was done after each distal anastomosis at a flow of 250 mL/min for 2 minutes.

An insulator pad (Shiley Inc, Irvine, CA) was placed behind the heart, and topical cooling with iced slush was applied in all patients to lower myocardial temperature initially and during the period of each reinjection. Systemic rewarming was commenced during construction of the final distal anastomosis. Early progressive reperfusion through the vein grafts was started by connecting one limb of the cardioplegic connector to the arterial cannula before the aorta was unclamped. All distal anastomoses were done during a single interval of aortic clamping, and the aortic anastomoses were done with tangential aortic clamping while the heart was reoxygenated and kept in the beating empty state.

Other than the cardioplegic solution used, the conduct of each operation was identical. There were no differences in mean total pump time or aortic cross-clamp time. The left internal mammary artery was used liberally, even in high-risk and elderly patients. The flow in internal mammary arteries and vein grafts was measured on bypass immediately after completion of the proximal anastomoses while the patient was rewarmed to 36.5°C. An electromagnetic flowmeter (Gould Statham SP 2204, Oxnard, CA) and a Doppler ultrasound flowmeter (Scimed OP DOP 130, Bristol, UK) were used.

For inotropic support during the weaning process, dopamine was used as the initial drug. Clinically significant inotropic support was defined as the need for more than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine or the need for epinephrine in any dose. When these pharmacologic agents failed, intraaortic balloon counterpulsation was instituted. Overall myocardial function was assessed by evaluating changes in prearrest and postarrest cardiac output, left ventricular stroke work index, need for vasopressor support, incidence of low output syndrome, and indicators of perioperative infarction. A series of postoperative hemodynamic profiles were recorded. The early postoperative assessment was made upon the arrival of the patient at the intensive care unit. The measurements were repeated 4 hours later and on the morning after the operation, approximately 18 hours postoperatively. Data were expressed as percent of the preoperative value for each patient. Sequential measurements of the myocardial isoenzyme of creatine kinase were obtained at specific times. A myocardial fraction greater than 50 IU/L between 18 and 30 hours after operation was considered diagnostic of myocardial injury [5]. A diagnosis of myocardial infarction was made when a new Q wave observed on the electrocardiogram was associated with an elevated level of the MB isoenzyme of creatine kinase.

Data were stored on a computer and analyzed using Statgraphics software package (Statistical Graphics Corporation, STSC, Inc, Rockville, MD) and procedures developed on SC statistical software (Lambda-Plus, Gembloux, Belgium). Values are presented as mean ± standard error of the mean. When comparisons were made between crystalloid and blood groups at specific points in time, the two-sample t test was used to determine significance. Other clinical data were compared by Mann-Whitney test, χ^2 test, or Fisher exact test when appropriate. Correlation was assessed by linear correlation coefficients. A multiple linear regression analysis was performed to simultaneously compare the influence of clinical and hemodynamic preoperative variables (including the type of cardioplegic solution) on left ventricular function after bypass.

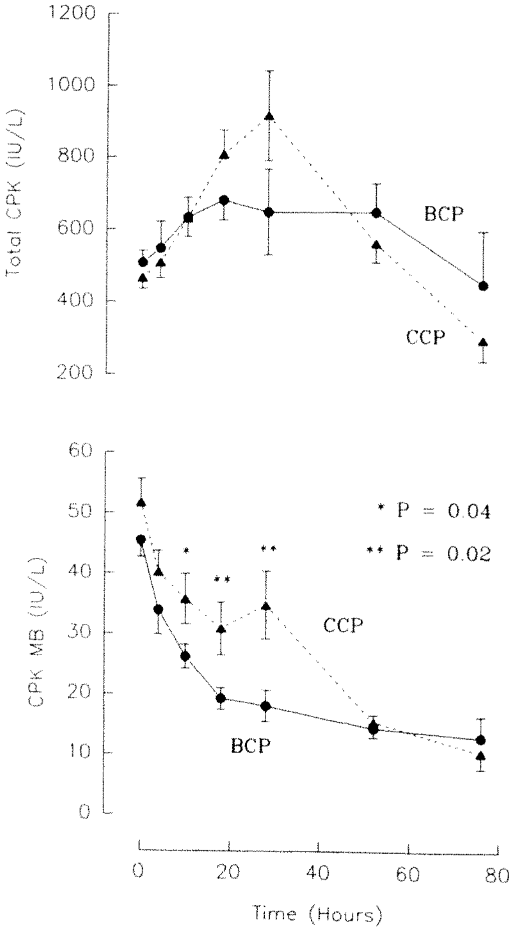

Fig 1. Comparison of myocardial enzyme release: systemic blood levels of the total creatine kinase and of the myocardial-specific isoenzyme (CPK-MB) at intervals after admission in the intensive care unit. Mean values are shown ± the standard error of the mean. (BCP = blood cardioplegia; CCP = crystalloid cardioplegia.)

Results

Clinical Outcome

There were three hospital deaths in the CCP group and none in the BCP group (not significant). One patient died of a major stroke, the second died suddenly on the third postoperative night probably because of arrhythmia, and the last patient was in cardiogenic shock on counterpulsation preoperatively and died of multisystemic organ failure. The incidence of myocardial infarction was low in both groups (BCP, 4.8%; CCP, 3.7%). The release of the MB isoenzyme of creatine kinase was significantly less between 12 and 30 hours after operation in the BCP group (Fig 1). Five patients (4 in the CCP group and 1 in the BCP

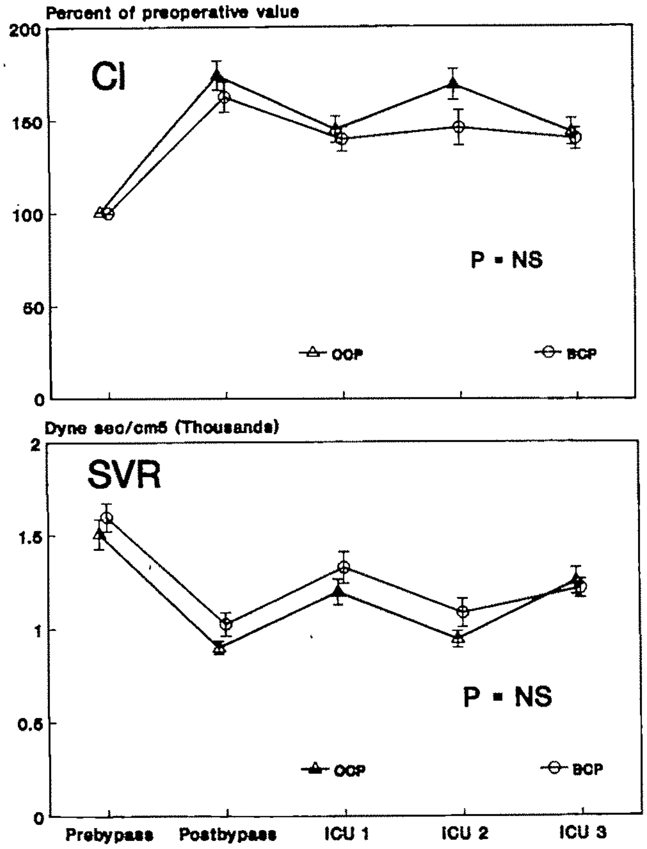

Fig 2. Effect of crystalloid cardioplegia (CCP) *and blood cardioplegia* (BCP) *on cardiac index* (CI) *and systemic vascular resistance* (SVR). *Mean values are shown ± the standard error of the mean.* (ICU 1 = *on arrival in intensive care unit;* ICU 2 = *4 hours postop;* ICU 3 = *morning after operation [≈18 hours postop];* NS = *not significant.)*

group) had a creatine kinase-MB level greater than 50 IU/L. Two patients in the BCP group and 2 patients in the CCP group needed intraaortic balloon counterpulsation. Twelve patients in the BCP group (28.6%) needed inotropic support versus 14 patients in the CCP group (25.9%). Permanent heart block occurred in 3 patients (7.1%) in the BCP group and in 2 patients (3.7%) in the CCP group (not significant). The frequency of new-onset postoperative atrial fibrillation or flutter was greater in the BCP group (28.6% versus 14.8%), but the difference was not significant.

Hemodynamic Data

Hemodynamic outcome is expressed in Figures 2 and 3. Cardiac index and left ventricular and right ventricular stroke work indexes increased markedly in the immediate postbypass period and subsequently stabilized at a lower value. Conversely, there was a decrease in systemic vascular resistance in the immediate postbypass period, followed by a trend toward stabilization at prebypass values. Afterload was assessed by systemic vascular resistance and pulmonary vascular resistance and never differed among the groups. Likewise, preload determined by wedge pressure and central venous pressure was similar among the groups. There were no significant differences between the BCP and CCP groups regarding cardiac index and left ventricular stroke work index. However, the percent value of right ventricular stroke work index was lower in the BCP group 4 hours postoperatively (120% ± 13% versus 175% ± 18%; $p = 0.036$).

In a group of patients selected on the basis of reduced prebypass left ventricular function (left ventricular stroke work index less than 40 $g \cdot beat^{-1} \cdot m^{-2}$) we found an inverse linear correlation (Fig 4) between duration of aortic cross-clamping and percent value of left ventricular stroke work index ($r = -0.441$; $p = 0.045$) after use of CCP (20 patients). Conversely, there was no correlation in the BCP group (21 patients) ($r = 0.125$; $p = 0.587$) (Fig 5).

A multivariate analysis was conducted to find the variables that influenced the immediate postbypass left ventricular function expressed as percent of prebypass left ventricular stroke work index. Multiple linear regression analysis selected hemodynamic variables such as prebypass right ventricular stroke work index ($p < 0.001$), prebypass systemic vascular resistance ($p < 0.001$), and postbypass pulmonary vascular resistance ($p < 0.005$) but the type of cardioplegia was not a significant factor.

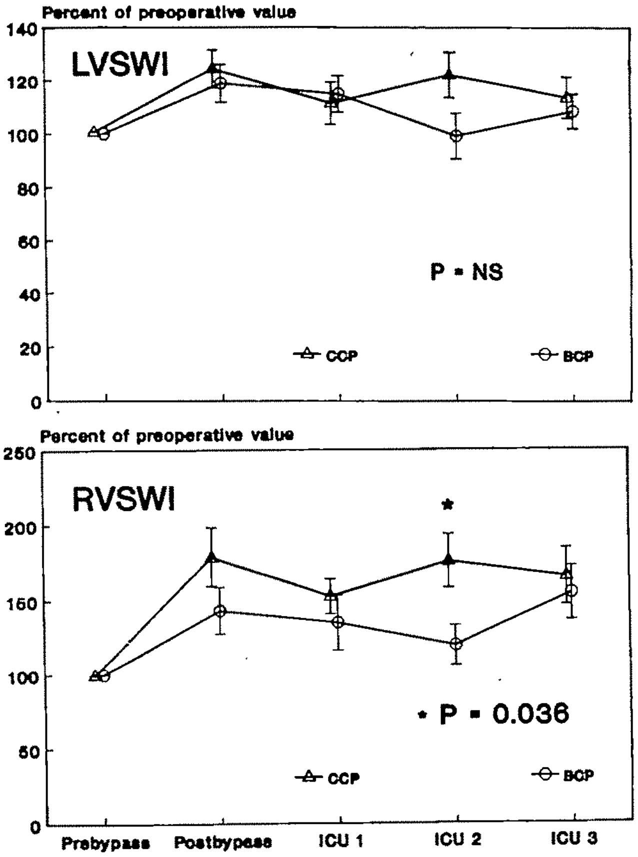

Fig 3. Effect of crystalloid cardioplegia (CCP) *and blood cardioplegia* (BCP) *on left ventricular* (LVSWI) *and right ventricular* (RVSWI) *stroke work index. Note that RVSWI is significantly lower* ($p = 0.036$) *4 hours postoperatively in the BCP group. Mean values are shown ± the standard error of the mean.* (ICU 1 = *on arrival in intensive care unit;* ICU 2 = *4 hours postop;* ICU 3 = *morning after operation [≈18 hours postop];* NS = *not significant.)*

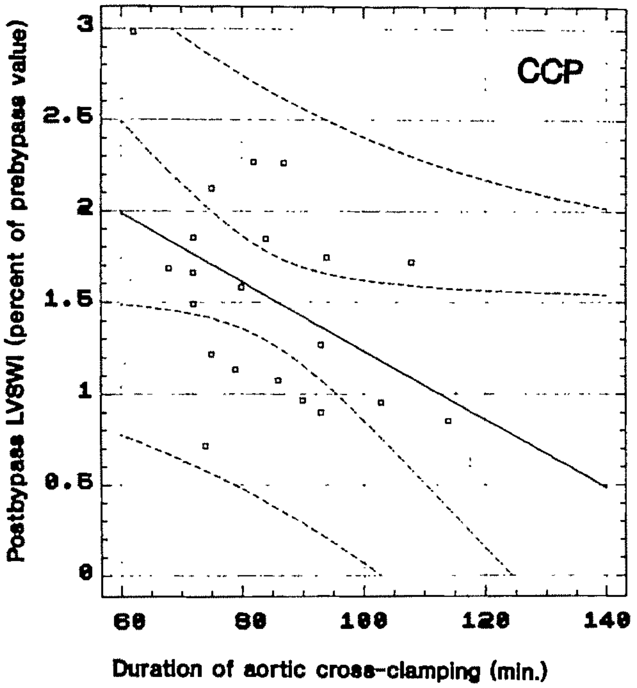

Fig 4. Inverse linear correlation between duration of aortic cross-clamping and postbypass left ventricular stroke work index (LVSWI) *expressed as percent of prebypass value in a group of 20 patients having reduced prebypass left ventricular function (LVSWI* < 40 $g \cdot beat^{-1} \cdot m^{-2}$*) and undergoing crystalloid cardioplegia* (CCP). $Y = 3.118 - 0.019X$; $R = -0.441$; $p = 0.045$. *The 95% confidence bands are the* dotted lines *closest to the regression line.*

Flow Determination in Bypass Grafts

Results of flow determinations in bypass grafts are depicted in Table 3. The average additional flow provided by revascularization is 148.9 ± 14.2 mL for BCP and 135.5 ± 17.4 mL for CCP ($p = 0.549$). Detailed flow determinations made in the different grafts did not show significant differences among the groups except for flow in the grafts supplying the posterior descending arteries.

Fluid and Blood Balance

Operative fluid balance was computed by including the amount of priming, colloids, and cardioplegic solution, and substracting urinary output (Fig 6). Of course, the initial and additional volume of CCP solution used was much lower in the BCP group (894.1 ± 16.6 versus 2,171.3 ± 41.1 mL; $p < 0.001$). This resulted in a net fluid balance reduced by more than 50% in the BCP group (1,526.7 ± 86.5 versus 3,511.3 ± 148.2 mL; $p < 0.001$). The total volume of blood administered did not differ significantly among the groups.

Comment

The addition of potassium ion in the range of 16 to 35 mEq/L to an isosmolar cardioplegic solution is currently advocated [1, 6]. Yet, repeated infusions of high concentration of potassium ion may be damaging to the conduction system, as a much higher incidence of atrioventricular dissociation arrhythmias was noticed when hearts were reperfused with cardioplegic solutions containing 20 mEq/L of potassium after each distal anastomosis [7].

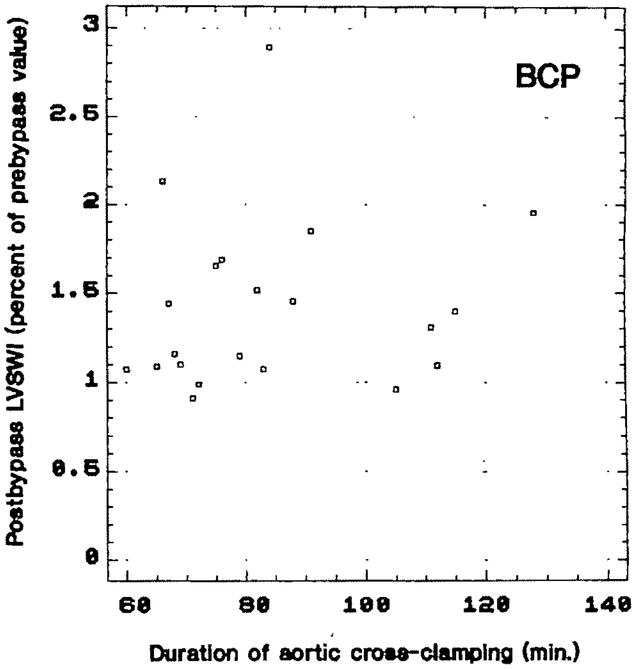

Fig 5. There was no correlation between duration of aortic cross-clamping and postbypass left ventricular stroke work index (LVSWI) *expressed as percent of prebypass value in a group of 20 patients having reduced prebypass left ventricular function (LVSWI* < 40 $g \cdot beat^{-1} \cdot m^{-2}$*) and undergoing blood cardioplegia* (BCP).

Table 3. Flow Determinations in Bypass Grafts

Variable	Blood Flow (mL/min)	Crystalloid Flow (mL/min)	p Value
LIMA free flow	113.8 ± 10.6 (n = 39)	123.5 ± 7.1 (n = 52)	0.433
LIMA on LAD	61.4 ± 5.2 (n = 34)	50.9 ± 10.2 (n = 28)	0.336
SV diagonal	70.9 ± 18.8 (n = 10)	66.6 ± 7.5 (n = 7)	0.856
SV marginal 1	52.4 ± 9.7 (n = 18)	54.7 ± 7.8 (n = 18)	0.852
SV marginal 2	41.1 ± 5.3 (n = 14)	30.8 ± 9.4 (n = 6)	0.323
SV marginal 3	65.2 ± 22.3 (n = 2)	38.0 ± 20.0 (n = 6)	0.540
SV RCA	49.0 ± 7.3 (n = 10)	68.0 ± 7.6 (n = 11)	0.084
SV post desc	34.0 ± 4.8 (n = 18)	61.1 ± 11.5 (n = 14)	0.024
Flow/patient	148.9 ± 14.3 (n = 39)	135.5 ± 17.4 (n = 35)	0.549

LAD = left anterior descending artery; LIMA = left internal mammary artery; post desc = posterior descending artery; RCA = right coronary artery; SV = saphenous vein.

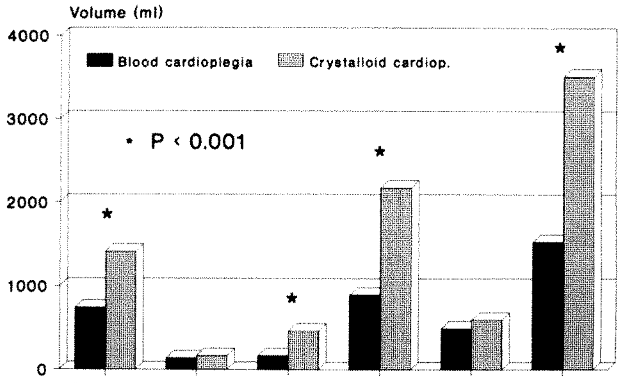

Fig 6. Operative fluid balance.

Furthermore, a high concentration of potassium in cardioplegic solutions plays a critical role in causing functional endothelial damage and could be harmful while perfusing saphenous vein grafts [8]. Induction of cardiac arrest with an initial high-potassium concentration followed by maintenance with low-potassium cardioplegia was used more recently [9]. Throughout our study, low-potassium cardioplegia provided adequate cardiac arrest during prolonged periods of aortic cross-clamping. The incidence of permanent heart block was low in both the BCP and CCP groups.

Given the insensitivity of clinical variables and the larger proportion of high-risk patients found in our BCP group, the hemodynamic data of the present study must be considered cautiously. Therefore, the data were transformed and expressed as a percentage of the control (prearrest value) to allow for individual differences in the initial measurement, and a multivariate analysis was applied. Results indicated that left ventricular function was equally maintained in both groups. Right ventricular function was significantly inferior in the BCP group 4 hours after aortic unclamping (see Fig 3). This finding corroborates the work of Mullen and colleagues [2], who demonstrated that BCP provided excellent protection for the left ventricle but that CCP produced colder right ventricular temperatures and better postoperative right ventricular function. Furthermore, we hypothetize that lesser protection of the right ventricle can explain an increase in vascular resistance in that territory and the lower flow observed with BCP in the vein grafts supplying the right coronary system (main trunk and posterior descending artery).

The extent of myocardial ischemic damage has been thought to be determined principally by the duration of aortic clamping. Our data demonstrate, at least in patients with impaired preoperative left ventricular function, a negative correlation between duration of aortic cross-clamping and postbypass left ventricular performance in CCP but not in BCP. This confirms other studies [10] suggesting that BCP may be advantageous in patients with impaired left ventricular function requiring procedures with prolonged aortic cross-clamp time. The significantly lower release of creatine kinase-MB isoenzyme observed with BCP between 12 and 30 hours after operation corroborates this fact. By this time these criteria are of particularly high diagnostic value as most of the low-level creatine kinase-MB activity seen in the very early postoperative period has disappeared from the serum [5, 11].

Because of concern about red blood cell sludging, it has been recommended that BCP solutions be administered at 20°C, as further cooling might lead to these undesirable effects [12]. However, the potential danger of sludging at low temperatures (6° to 8°C) is avoided by using hemodilution of the BCP solution (hematocrit, 0.15 to 0.20), and experimental studies showed that red cell sludging is not a determinant of flow of BCP solution at 10°C if the hematocrit is 0.20 or less [13]. In contrast, the addition of red cells to a cardioplegic solution might improve capillary perfusion distribution [14]. The rheologic effect of added red cells was confirmed by the maintained perfusion of the canine posterior papillary muscle [15] and by clinical data [16]. Conversely, studies on regional myocardial blood flow showed a maldistribution of CCP with respect to subendocardium [17]. It should be noted that flow was measured in normal coronary beds in these studies and flow across diseased coronary arteries was not tested with high-hematocrit cardioplegia.

The risk of cryoprecipitation in patients with cryoglobulinemia is an additional concern [18, 19] but can be eliminated by routine screening. Indeed, current laboratory methods are able to detect cold-agglutinating autoantibodies, taking into account the extremely low temperatures that the heart and body may attain during cardiopulmonary bypass, as described by Moore and colleagues [20]. The risk of disastrous cryoprecipitation in patients with cryoglobulinemia is often mentioned in the literature, but data on the exact incidence of the latter complication and its in vitro detection are lacking. Our study shows that cold antibodies at a clinically significant titer were detected by routine screening in about 10% of the patients. Administration of CCP and a systemic moderate hypothermia of 28°C during cardiopulmonary bypass were the measures taken in these cases. There was no evidence of hemolytic or vascular occlusive crisis.

The power of the study was insufficient to have found a significant difference in clinical outcome. From the end of this investigation, 159 patients were operated on for triple-vessel disease using BCP. Although these patients belonged predominantly to a high-risk population (one risk factor, 24.5%; two or more risk factors, 39.0%), the hospital mortality rate was only 1.9%. Death was caused by pulmonary embolism, uncontrollable bleeding after redo operation, and renal insufficiency but never by low output syndrome as the prime reason.

Low-potassium BCP is now our preferred method of myocardial protection. It offers several obvious advantages over crystalloid solutions: myocardial injury is reduced as demonstrated by a lower release of creatine kinase-MB isoenzyme and there is less risk of fluid overload when large volumes are required. Given the methodological limitations of this observational study, we were not able to demonstrate a clear superiority of BCP over

CCP regarding preservation of left ventricular function, the absence of randomization affecting negatively the BCP group. Nevertheless, our data suggest that BCP may be advantageous in patients with impaired left ventricular function requiring prolonged aortic cross-clamp time.

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Management of Dysfunction in the Transplanted Lung: Experience With 7 Clinical Cases

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In a series of 34 lung transplant patients, donor lung dysfunction occurred on 7 occasions. One patient underwent retransplantation and the remaining 6 were treated conservatively. Survival was 100% in the donor lung dysfunction group. Percent predicted forced expiratory volume in 1 second, carbon monoxide diffusion, room air oxygen tension, and distance walked in 6 minutes were all lower ($p < 0.05$) at 1 month after transplantation in those patients with donor lung dysfunction as compared with those without. These differences were not significant at 3 months after transplantation. We conclude that donor lung dysfunction can usually be managed conservatively with satisfactory results. Longer follow-up of this group of patients will be necessary to determine the long-term consequences of early graft injury.

(Ann Thorac Surg 1992;53:635–41)

Lung transplantation has proved to be an effective and durable procedure for the treatment of end-stage pulmonary disease [1]. The number of patients receiving lung transplantation is increasing rapidly, and the incidence of morbidity and mortality is showing a decline at most active centers. However, despite improvements in preservation and technique, there continues to be a group of patients with poor donor lung function from the onset or as a result of a complication. A clinical dilemma arises in how best to manage these difficult patients, namely, when should conservative management cease and retransplantation be performed? Recently, at our institution we have had experience with the management of 7 such patients. The purpose of this report is to describe their clinical course and to detail the changes in pulmonary function testing that occurred during follow-up. A contemporaneous group of lung transplant recipients whose recovery did not include donor lung dysfunction (DLD) have been included in the results section as a comparison group.

Patients and Methods

During the 12-month period ending June 1990, 34 patients underwent 35 lung transplantations, 7 of whom exhibited persistent DLD. This diagnosis was made because of the increased alveolar to arterial gradients, decreased lung compliance, persistent diffuse chest roentgenographic infiltrates, prolonged periods in the intensive care unit, and on many occasions biopsy evidence of diffuse alveolar damage. Patients with phrenic nerve palsy or episodes of lower lobe collapse that were slow to resolve were not included in this group. A cohort of 23 other lung transplant recipients (of the remaining 27) were chosen as a comparison group. Two patients who were ventilated before operation have been excluded along with 2 other patients who died on postoperative day 3 and postoperative day 48. None of these 4 patients suffered from DLD, but they were not believed to be representative of a "normal" posttransplantation recovery.

Six of the 7 DLD patients were treated conservatively, whereas 1 underwent retransplantation. The management of the patients treated conservatively consisted of continued ventilator support where necessary and attention to detail in the prevention of sputum retention and pulmonary sepsis. Regular aggressive chest physiotherapy and bronchoscopy as required were the mainstays of pulmonary care. Nutrition was maintained by the use of parenteral intravenous alimentation.

Immunosuppression followed our usual protocol, with preoperative azathioprine at a dose of 2 mg/kg followed in the postoperative phase by daily administration of azathioprine at the same dose. Cyclosporine was initially given as an intravenous infusion monitored by blood levels, and Minnesota antilymphoblast globulin provided the third limb of our regimen. Regular steroids were withheld until several days into the postoperative phase. In essence, the usual intensive supportive therapy was maintained for as long as required.

We have found that the combination of lung dysfunction and prolonged ventilatory assistance may make the weaning process more difficult. In several cases, weaning attempts were suspended and emphasis was placed on mobilization and ambulation with mechanical ventilatory

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Table 1. Patient Characteristics

Patient No.	Age (y)	Diagnosis	Tx Type
Donor lung dysfunction			
1	55	COPD	LS
2	50	LAM	LS
3	43	IPF	LS
4	41	PPH	RS
5	60	COPD	LS
6	32	PPH	RS
7	21	CF	BLT
No dysfunction group			
1	47	COPD	RS
2	46	COPD	RS
3	57	COPD	LS
4	51	COPD	RS
5	49	COPD	BLT
6	30	CF	BLT
7	56	COPD	RS
8	36	PPH	RS
9	53	COPD	LS
10	31	PPH	RS
11	48	COPD	BLT
12	35	COPD	RS
13	34	CF	BLT
14	51	COPD	BLT
15	54	COPD	RS
16	58	COPD	LS
17	44	COPD	BLT
18	54	COPD	BLT
19	36	ASD Eisen	RS
20	29	PPH	LS
21	48	COPD	BLT
22	43	IPF	RS
23	42	COPD	BLT

ASD Eisen = atrial septal defect with Eisenmenger's syndrome; BLT = bilateral lung transplant; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis; LAM = lymph angioleiomyomatosis; LS = left single; PPH = primary pulmonary hypertension; RS = right single; Tx = transplant.

assistance. Once the patient's stamina improved, weaning was resumed and was rapidly accomplished.

Patient Information

The descriptive data for each patient in the two groups are listed in Table 1. Apart from the difference in numbers in the two groups, there are proportionately fewer double-lung transplant recipients and fewer patients with chronic obstructive pulmonary disease in the DLD group.

Follow-up

All 7 patients experiencing DLD have survived and have reached 6 months of follow-up. In the comparison group, all patients have survived at least 6 months.

Pulmonary Function Testing

Each patient undertook pulmonary function testing (including room air blood gases) at the time of evaluation for transplantation and at regular intervals in the postoperative period. For consistency, the points of comparison have arbitrarily been chosen at 1, 3, and 6 months.

Included in the testing was a standardized 6-minute walk, measuring the total distance traveled in that time. Supplemental oxygen was administered as necessary to keep the oxygen saturations greater than 90%.

Differences between the two groups have been analyzed in terms of room air arterial blood gases, forced expiratory volume over 1 second, carbon monoxide diffusion capacity, and the distance walked in 6 minutes.

Statistics

Unless otherwise stated, all results are expressed as mean ± 95% confidence limits. Significant differences were accepted between any two groups when the confidence limits were nonoverlapping.

Results

Patient Survival

All patients in both groups have survived at least 6 months, and none requires supplemental oxygen.

Mechanism of Lung Injury

Donor lung dysfunction developed in three distinct circumstances. Two patients had obstruction at the level of the pulmonary venous anastomosis, and this almost certainly explains the occurrence of their severe dysfunction postoperatively. The first of these patients (who had chronic obstructive pulmonary disease) also sustained an intraoperative myocardial infarction and required an intraaortic balloon pump and intensive inotropic support for several days after the operation. In this patient the diagnosis of pulmonary venous anastomotic stenosis was made early in the postoperative period by lung scan and right heart catheter study. Unfortunately, this patient's condition was so unstable that it was not until the seventh postoperative day that reoperation and placement of a pericardial patch to the pulmonary venous anastomosis was possible. Pathological examination of the open lung biopsy taken at this procedure suggested that the lung was irreversibly damaged, and this conclusion was consistent with his subsequent clinical picture. Despite an improvement in perfusion of the transplant lung he continued to require an inspired oxygen fraction of 0.80 to maintain arterial oxygen saturations greater than 90%. A second transplantation was successfully performed on postoperative day 11.

The second patient (who had primary pulmonary hypertension) had the pulmonary veins of her graft damaged at the time of harvesting the heart. Narrowing of what was a difficult pulmonary venous anastomosis occurred, with the diagnosis being made when she failed to be weaned from cardiopulmonary bypass. A pericardial patch was applied to the venous anastomosis, but serious lung injury had occurred at this stage. She required

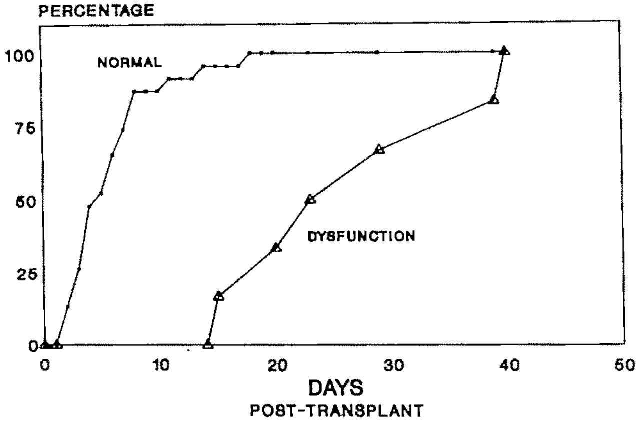

Fig 1. The time taken to achieve a room air oxygen tension greater than 60 mm Hg is illustrated for the groups with and without donor lung dysfunction.

extracorporeal membrane oxygenation for 3 days postoperatively, from which she was successfully weaned.

Three other patients sustained no apparent intraoperative complication that would have predisposed them to donor lung injury, yet dysfunction developed in the immediate postoperative period.

The two remaining patients demonstrated normal graft function in the immediate posttransplant period, but dysfunction developed in them as a result of a complication. One of these 2 patients required prolonged resuscitation after an unexpected cardiac arrest on the second postoperative day. Dysfunction developed in the second patient as a result of an airway complication on day 17 after transplantation.

Time in Intensive Care

For the group with DLD the mean time in the intensive care unit was 18.8 days (range, 7 to 36 days), which was significantly longer than the comparison group, which had a mean stay of 3.3 days (range, 1 to 6 days).

Pulmonary Function Testing

BLOOD GASES ON ROOM AIR. For the group with donor lung dysfunction the mean time to achieving an oxygen tension greater than 60 mm Hg on room air was 23.7 days (range, 15 to 40 days). This was significantly longer than for the comparison group, for which the mean time was 6.0 days (range, 2 to 18 days) (Fig 1). The room air oxygen tension measurements were significantly lower in the DLD group at 1 month, whereas at 3 and 6 months no significant difference was seen in comparison with the other group (Fig 2).

FORCED EXPIRATORY VOLUME IN 1 SECOND. At evaluation, 3 months, and 6 months there was no significant difference between the two groups in percent predicted forced expiratory volume in 1 second, whereas at 1 month the difference was significant (see Fig 2).

CARBON MONOXIDE DIFFUSION. A significant difference between the groups for percent predicted carbon monoxide diffusion was present at 1 month but not at evaluation, 3 months, or 6 months (see Fig 2).

SIX-MINUTE WALK DISTANCE. A significant difference in distance walked in 6 minutes was present between the groups at 1 month after transplantation but not at evaluation or at 3 and 6 months after transplantation (see Fig 2).

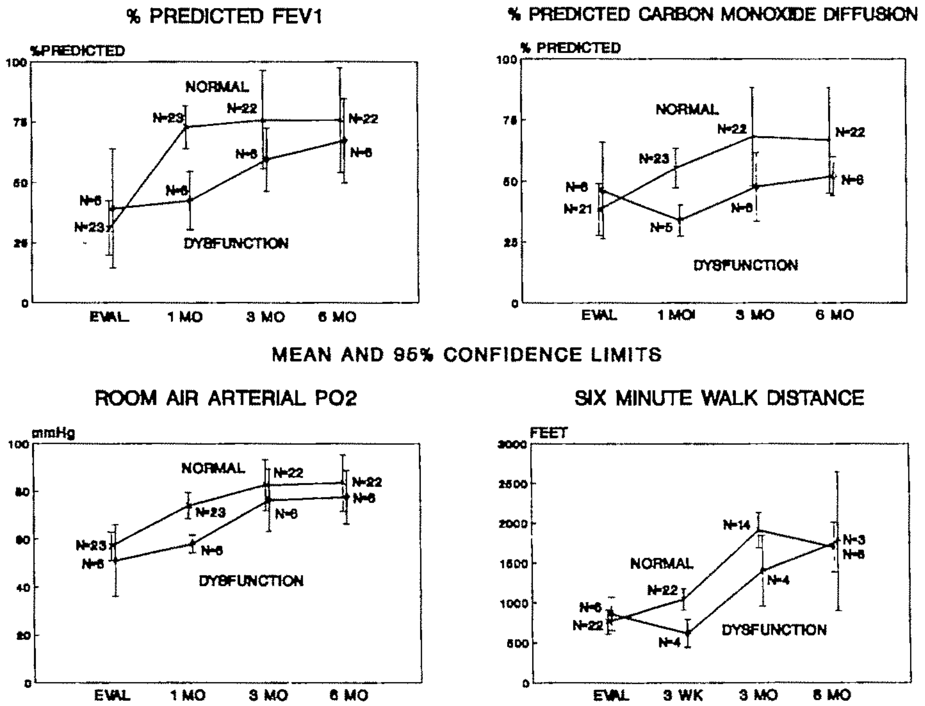

Fig 2. Mean and 95% confidence limits for percent predicted forced expiratory volume in 1 second (FEV1), percent predicted carbon monoxide diffusion (DLCO), room air oxygen tension (PO2), and 6-minute walk distance are given for the groups with and without donor lung dysfunction. (EVAL = evaluation.)

Table 2. Pulmonary Function Test Results for the 1 Patient With Donor Lung Dysfunction Who Underwent Retransplantation

Variable	Evaluation	1 mo	3 mo	6 mo
%pred FEV_1	16.7	41.2	31.9	35.1
%pred DLCO	25.1	48.8	27.6	51.2
Room air PO_2 (mm Hg)	73	89	84	70
6-min walk (ft)	905	900	1,721	1,711

DLCO = carbon monoxide diffusion; FEV_1 = forced expiratory volume in 1 second; PO_2 = oxygen tension; %pred = percent predicted.

At 3 and 6 months of follow-up, no patient in either group required supplemental oxygen to complete the walk. At 1 month after transplantation all but 1 of the patients in the DLD group required supplemental oxygen to keep the arterial saturations greater than 90% (mean, 3.5 L/min; range, 0 to 8 L/min), whereas only 3 of the 23 patients in the comparison group required oxygen supplementation (mean, 0.3 L/min; range, 0 to 3 L/min). The pulmonary function test results for the 1 patient in the DLD group who underwent retransplantation have been listed in Table 2.

Ischemic Times

There was no difference in the ischemic times between the two groups (DLD group, 282 ± 92 minutes; non-DLD group, 322 ± 28 minutes).

Donor Information

There was no difference in the mean age or incidence of a smoking history in the donor group. The time between lethal injury or event and eventual donation was the same for both groups, as was the occurrence of serious hypotension requiring resuscitation during this time. The requirements for inotropic support in the groups was essentially the same, although 2 donors in the nondysfunctional group did require α-agonist support (Table 3).

Table 3. Donor Population

Variable	Donor Lung Dysfunction	No Dysfunction Group
Number	7	21[a]
Age (y)	27.1 (± 10.1)	26.3 (± 8.5)
Smoking	3/5	10/17
Interval (d)[b]	1.5 (± 1.2)	2.0 (± 1.9)
Hypotension[c]	2	6
Dopamine dose[d]	8 (range, 0 to 12)	7 (range, 0 to 15)

[a] In two instances a single donor provided lungs for two recipients. [b] Interval from lethal event to organ donation. [c] Number with systemic hypotension (<80 mm Hg) requiring resuscitation before donation. [d] Dopamine infusion rate in micrograms per kilogram per minute.

Chest Roentgenogram

Examples of the chest roentgenographic appearances of a patient with DLD are given in Figure 3. The sequential improvement in the lung fields can take several months to occur, and often functional improvement occurs before the roentgenographic changes.

Lung Scan Information

On one occasion the lung perfusion scan was found to be useful in diagnosing the cause of DLD. The case involved was one with pulmonary venous anastomotic stenosis. On the first postoperative day, the perfusion to the donor lung was 6% of total pulmonary arterial flow. This had risen to 11% by the sixth postoperative day and to 48% the day after a pericardial patch was applied to the pulmonary venous anastomosis.

In a second patient, a single-lung transplant recipient with idiopathic pulmonary fibrosis, the lung scan showed 29% perfusion of the transplanted side. This was associated with serious DLD. A pulmonary angiogram was performed, and the pulmonary capillary wedge pressure was believed to be higher on the transplanted side than on the nontransplanted side. Concern was present that pulmonary venous obstruction was present, and the patient was returned to the operating room for measurement of the gradient across the anastomosis and revision as appropriate. At the time of reexploration the anastomosis was wide open with no gradient. The lung looked inflamed and edematous, and an open lung biopsy was performed. This revealed diffuse alveolar damage. Immediate postoperative and then daily quantitative perfusion scans were performed, and these demonstrated a gradual improvement to the transplanted side (Fig 4).

In the remainder of the patients in this series there was no correlation between the percentage perfusion to the donor lung and the quality of donor lung function.

Comment

Although most patients have satisfactory donor lung function after transplantation there is still a substantial minority in whom moderate to severe dysfunction develops.

In this series of patients there were three distinct mechanisms of donor lung injury: early dysfunction as a result of a technical complication, early dysfunction without an obvious precipitating event, and delayed dysfunction as a result of a postoperative complication. The pulmonary venous obstruction that occurred in 2 patients is a technical problem that should be avoidable. The damage to the pulmonary veins during harvesting of the lungs in the second patient should not occur with proper understanding between the cardiac and pulmonary retrieval teams. The results outlined here reveal the critical importance of a wide open pulmonary venous anastomosis. We believe that the key step to obtaining this is to keep the clamp well back on the atrium and to carefully fashion a suitable recipient atrial cuff. If there is any doubt about the sufficiency of the anastomosis, then intraoper-

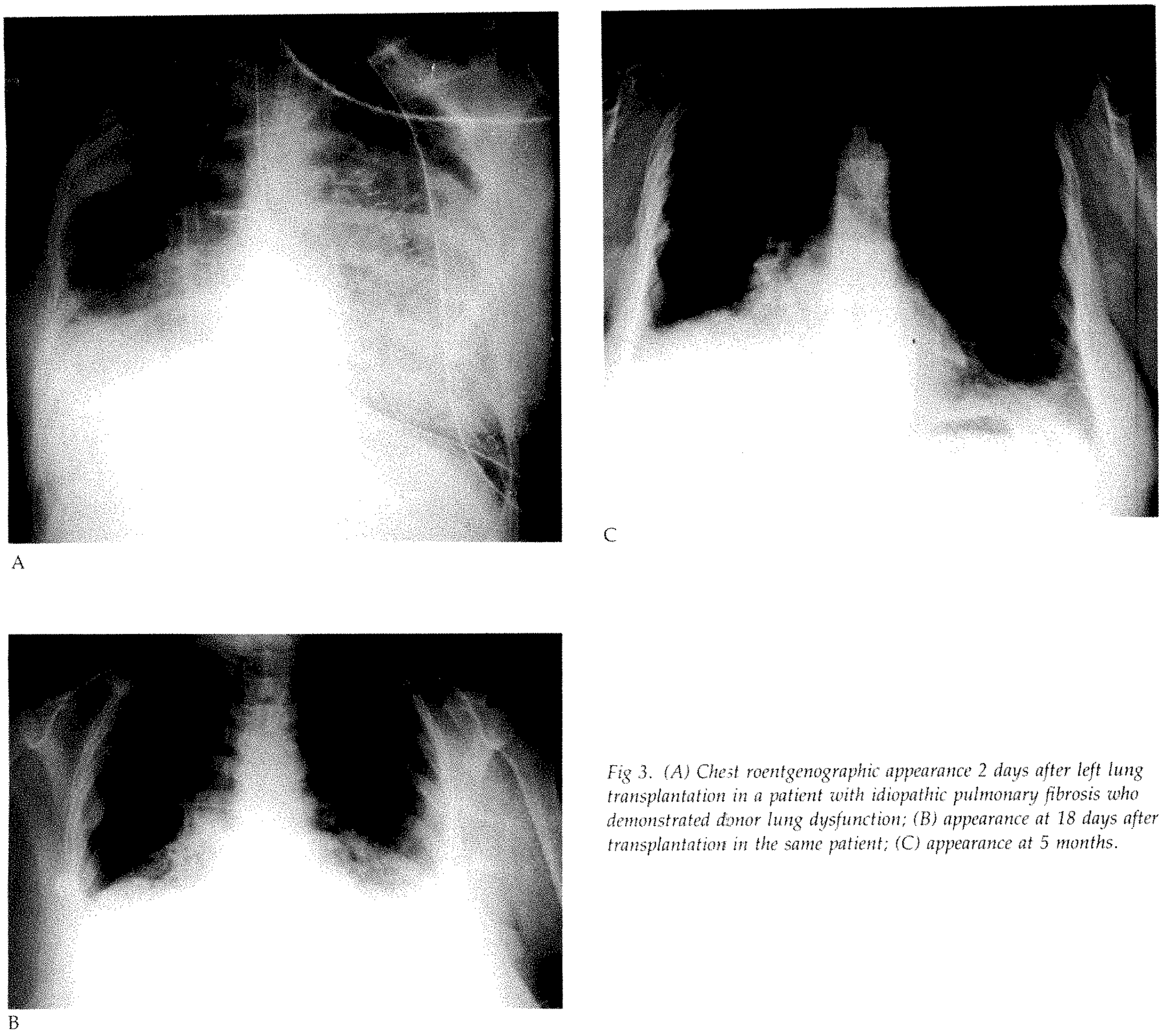

Fig 3. (A) Chest roentgenographic appearance 2 days after left lung transplantation in a patient with idiopathic pulmonary fibrosis who demonstrated donor lung dysfunction; (B) appearance at 18 days after transplantation in the same patient; (C) appearance at 5 months.

ative measurement of the pressure gradient across the anastomosis should be obtained.

The two patients in whom lung injury developed in the postoperative period both demonstrated good lung function before the complication that gave rise to the insult. Both had been extubated and discharged from the intensive care unit. The transplanted lung may well be more susceptible to injury than normal lung in the postoperative period. The course of these 2 patients was similar to that of nontransplant patients recovering from adult respiratory distress syndrome.

There remains a group of patients (3 in this series) in whom DLD developed despite a straightforward operative course. The possible mechanisms behind such injuries would include unrecognized lung injury sustained before retrieval, poor preservation technique, unrecognized pulmonary arterial or venous obstruction, bronchial obstruction, severe early rejection or infection, or possibly oversizing of the donor lung. Brain death developed in 2 of the 3 donors in this group after head trauma. With this mechanism of death, aspiration is a definite possibility. In addition, the retrieval of these organs occurred within 24 hours of donor injury on both occasions, a time when the DLD from unrecognized aspiration may not have reached its nadir at the time of retrieval. In both cases the donor arterial oxygen saturations were greater than 450 mm Hg on 100% oxygen therapy and the bronchoscopies had been judged to be clear. In the third case in this group the retrieval process was precipitated by sudden cardiovascular collapse of the donor. The preservation process appeared to proceed without a problem but was more hurried than normal. This may have had some bearing on the subsequent dysfunction.

Rejection would appear to be an unlikely explanation for the events described, as dysfunction appeared within hours of operation and all 3 patients were treated with antirejection therapy without response. Consideration was given to possible technical deficits in relation to the

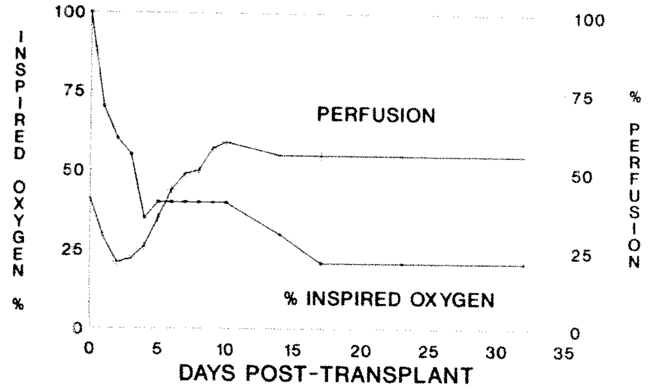

Fig 4. The percent perfusion to the transplanted lung and the inspired oxygen concentration required to maintain arterial saturation are illustrated for the patient whose roentgenograms are shown in Figure 3.

anastomoses. One patient did return to the operating room for an open lung biopsy and for measurement of pressure gradients across each vascular anastomosis. No gradients were detectable. The open lung biopsy revealed diffuse alveolar damage without rejection or infection. Bronchoscopies ruled out airway complications. No clinically important pulmonary infections developed in any of the 3 patients. Whether donor lung dysfunction can be induced by oversizing the donor in comparison to the recipient is uncertain. On two of the three occasions the donors were male, being 15.2 and 35.6 cm taller with weights 9.5 and 18.5 kg heavier than their two female recipients. Both were left single-lung transplants (1 for idiopathic pulmonary fibrosis and 1 for chronic obstructive pulmonary disease). Although disparities such as this have been present in other donor/recipient pairs without subsequent dysfunction, the limits to size compatibility in lung transplantation have yet to be determined.

The ischemic times in the patients with DLD were in fact shorter than average, and we have frequently gone more than 7 hours without DLD. It would seem unlikely that ischemic time by itself is a reason for the donor lung injury.

Recognition of donor lung dysfunction/injury may not take place until several hours into the postoperative period. It is our routine to obtain arterial blood gas measurements on 100% oxygen within 10 to 20 minutes of reperfusion of the donor lung(s). Unless the arterial oxygen saturations are poor at this stage there may be no reason to suspect a problem has occurred. Usually the inspired oxygen fraction is weaned down to 0.35 within hours of the operation. Suspicion of lung injury is raised when this is not possible. Further confirmation is obtained by the presence of infiltrates on the chest roentgenogram within 12 to 24 hours of the operation, as the chest roentgenogram usually remains relatively clear for the first 36 hours. On some occasions high levels of positive end-expiratory pressure are required to control pulmonary edema, and in these severe cases the clinical course is so abnormal that there is no doubt about the diagnosis.

In each of these patients consideration was given to retransplanting. However, donor lungs are usually not immediately available and a period of conservative management is inevitable even if the decision to retransplant is made. During such waiting periods it became clear to us that improvement in the donor lung function did occur, albeit slowly, and that with the inherent complexities and risks of retransplantation, conservative treatment was an attractive alternative.

The extent of chest roentgenographic infiltrates can fluctuate markedly during the recovery phase. Initially we treated all deteriorations in roentgenographic appearances as rejection episodes, but when repetitive bouts occurred it became clear that the fluctuations were often due to changes in fluid balance rather than infection or rejection.

Although survival is 100% for these patients, one has to be concerned with the consequences of such injury on long-term lung function. Admittedly our follow-up is short but it is encouraging to see that there is a favorable trend in each of the pulmonary variables measured (see Fig 2). The comparison group is not equivalent to the group with DLD. There are proportionately more bilateral lung transplant recipients and chronic obstructive pulmonary disease patients in the former group. Comparison of only the single-lung transplant recipients in each group, however, did not change any of the above conclusions. The reason for including the comparison group is to indicate what usually happens to the postoperative lung function tests in patients without DLD. Clearly the forced expiratory volume in 1 second and carbon monoxide diffusion levels do not reach 100% of predicted values after lung transplantation, even when those patients with DLD are excluded. The room air oxygen tension values and 6-minute walk distances do tend to approach normal limits by 3 to 6 months in both groups of patients.

Caution has to be applied to conclusions about the long-term results in the DLD group as the overall numbers are small and the chances of missing a significant difference (type 2 error) are therefore high. Although the DLD group are significantly below the comparison group at 1 month for all pulmonary variables measured, there is no difference seen at a later stage of follow-up. It appears likely that long-term impairment of pulmonary function tests would be expected after such diffuse and severe lung injury [2] if extrapolation from nontransplant patients is pertinent. However whether this translates to symptoms and reduced performance has yet to be determined. The American Thoracic Society published guidelines for the evaluation of impairment/disability secondary to respiratory disorders [3]. The DLD group, by the American Thoracic Society classification, would fall into the moderately impaired category when mean percent predicted forced expiratory volume in 1 second and carbon monoxide diffusion were examined at the 3- and 6-month stages of follow-up. This category correlated with diminished ability to meet the physical demands of many jobs. As pointed out by the American Thoracic Society, however, patients with identical levels of impairment may have different degrees of disability.

The patients in the DLD group are all now free of supplemental oxygen therapy and demonstrate an exercise endurance equal to many from the non-DLD group when 6-minute walk distances are compared. It is possible, when longer follow-up is available, that significant differences will be shown between the 6 conservatively treated DLD patients and those patients without DLD. Even if this is the case, the group as a whole has demonstrated 100% survival, which makes the chances of improving on these results with retransplantation somewhat unlikely. We have only 1 patient in this series who underwent retransplantation for DLD. He has had a complicated postoperative course, which has included repetitive bouts of cytomegalovirus infection. Because of this, comparison of his results with those of the conservatively treated DLD patients is unlikely to be helpful in determining which approach gives the best long-term result.

We conclude that severe donor lung dysfunction can usually be managed conservatively and that even a prolonged period of postoperative dysfunction is compatible with a good functional result.

The members of the Washington University Lung Transplantation Group are as follow: Thoracic Surgery—Joel D. Cooper, MD, Larry R. Kaiser, MD, Michael K. Pasque, MD, and Carolyn M. Dresler, MD; Pulmonary Medicine—Elbert P. Trulock, MD, and Neil A. Ettinger, MD; Anesthesiology—Anastasios Triantafillou, MD, Paul Heerdt, MD, Demetrios Lappas, MD, George Despotis, MD, Timothy Herbst, MD, Charles Hogue, MD, and Charles Pond, MD; Cardiology—Edward Fry, MD; Transplant Coordinators—Laura Ochoa, RN, Kate Sander, RN, and Dru Straatman, RN; Pulmonary Rehabilitation—Dottie Biggar, RN, Jill Malen, RN, Betty Mercer, RRT, Larry Sylvester, RRT, and Yvonne Sledge, CRTT; Physical Therapy—Tammy Versilus, RPT, and Kelly Walsh, RPT; Psychology and Psychiatry—Deborah Schlitt, PhD, and Saaid Khojasteh, MD; Social Work—Cina Robertson; Nutrition and Dietetics—Deborah Reinhart and Kathy Artkras; Pastoral Care—Cheryl Palmer.

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Cardiac Arrhythmias and Myocardial Ischemia After Thoracotomy for Lung Cancer

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The records of 598 patients undergoing a thoracic surgical procedure for lung cancer from 1975 through 1989 were reviewed for occurrence of cardiac arrhythmias and myocardial ischemic events. Atrial tachycardias occurred in 16% (94/598); atrial fibrillation was preponderant (87%), followed by supraventricular tachycardia and atrial flutter. Patients with recurrent episodes of dysrhythmias had a significantly higher mortality rate than those without episodes or with a single episode only (17% versus 2.4%; $p < 0.01$). Transient ischemic electrocardiographic changes were documented in 23 patients (3.8%) and myocardial infarction in 7 (1.2%). An abnormal preoperative exercise test result and intraoperative hypotension were strongly associated with both dysrhythmia and ischemia ($p < 0.01$). Pneumonectomy, ischemic changes on the electrocardiogram, and cardiac enlargement were also associated with arrhythmias ($p < 0.01$). A weaker association ($p < 0.05$) was found between postoperative arrhythmias and old myocardial infarction (>6 months), arterial hypertension, and heart failure. Pulmonary function had no predictive value in this respect. A history of angina or old myocardial infarction was predictive of transient postoperative myocardial ischemia but not myocardial infarction. Despite improved anesthetic and monitoring techniques and more frequent use of the intensive care unit postoperatively in the last decade, the incidence of arrhythmias after thoracotomy has not decreased. More effective prevention is needed, particularly for patients with defined preoperative and perioperative risk factors.

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Cardiac arrhythmias are well-recognized complications after noncardiac thoracic operations. These arrhythmias are usually of atrial origin; ventricular arrhythmias are uncommon. The reported incidence of atrial tachyarrhythmias after thoracic operations ranges between 10% and 28% [1–5]. Arrhythmias after pneumonectomy in particular may be associated with an increased mortality [4]. Various predictors of these arrhythmias have been sought, yet very few significant ones have been identified. Furthermore, myocardial infarction and cardiac failure associated with noncardiac thoracic operations are common causes of mortality and serious morbidity [5–8]. The purpose of this retrospective study was to analyze various preoperative and perioperative risk factors of cardiac complications in patients undergoing thoracic operations for carcinoma of the lung during a 15-year period and to assess their possible association with the occurrence of postoperative arrhythmias and myocardial ischemic events. During the past 10 years, monitoring techniques have improved. Therefore, we also compared patients operated on from 1975 through 1982 with those having operation from 1983 through 1989.

Material and Methods

The records of 598 patients who underwent a thoracic operation for carcinoma of the lung at our hospital from 1975 to the end of 1989 were reviewed. The history of cardiac symptoms, results of physical examination, electrocardiogram (ECG), chest radiograph, and results of pulmonary function tests and exercise testing were recorded. Preoperative arterial hypertension, a history of angina, time from prior known myocardial infarction, and evidence of previous nonrecognized infarction by Q waves on the ECG were also noted. Operation and anesthesia records were analyzed for factors having predictive value of perioperative cardiac risk.

In each patient, a 12-lead ECG was obtained before the operation and again postoperatively on the first morning; thereafter, serial ECGs were recorded whenever cardiac symptoms occurred or whenever changes were observed in the routine ECGs. Intraoperatively heart rhythm was recorded by oscilloscope ECG. The ECGs were analyzed for new arrhythmias or evidence of myocardial ischemia. The diagnosis of transmural myocardial infarction required new Q waves on the ECG of at least 0.04-second duration and 1 mm or more in depth. The diagnosis of nontransmural myocardial infarction was made when new or additional ST segment depressions or negative T waves or both developed, persisted for more than 48 hours, and were associated with elevation of the serum levels of the creatine kinase MB fraction. New T wave and ST segment depressions returning to normal within 48

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hours with or without concomitant anginal symptoms were designated transient myocardial ischemia. Eight patients with chronic atrial fibrillation on the ECG were excluded from the study.

Bicycle exercise testing was performed on an upright bicycle ergometer at an initial work load of 40 W. The work load increased in a stepwise fashion every sixth minute by 40 W until predicted maximal heart rate was obtained. The test was terminated 6 minutes after the maximal heart rate was achieved or at the onset of limiting dyspnea, chest pain, or fatigue. A positive response to exercise testing required horizontal or downsloping ST depression of at least 1 mm at 0.08 second after the J point, angina during or after the exercise, or both of these. The exercise test was performed by 557 patients (93%).

Before the operation, the patients underwent pulmonary function tests including total lung capacity, forced vital capacity, forced expiratory volume in 1 second, steady-state diffusing capacity, and bronchodilation test. In patients with marked ventilatory impairment, arterial blood gas analysis (arterial oxygen tension, arterial carbon dioxide tension) was performed at rest and during exercise. Measurement of regional pulmonary ventilation and perfusion was done using xenon 133 gas, and lung function remaining after lung resection was calculated with standard formulas.

The records relating to the operation and the anesthesia management were reviewed to obtain information concerning any cardiac complications that developed during the perioperative period. Intraoperative hypotension was defined as a decrease of 30% or more in systolic blood pressure from preoperative levels lasting for at least 10 minutes. Operative mortality was defined as death within 30 days after operation.

The patients were divided into two groups, those operated on during the 8-year period 1975 through 1982 (n = 290) and those during the 7-year period 1983 to the end of 1989 (n = 308) (Table 1). The only significant differences between the two groups were the greater number of female patients and the poorer lung function of patients in the latter period. Therefore, the analysis of risk factors was performed in the combined series of patients. Some details, such as evidence of previous paroxysmal atrial arrhythmia and distribution of cardiac events by days after operation, were documented in the latter series only. In the same period, more sophisticated methods of anesthesia management and intraoperative monitoring were available, and the intensive care unit was used more frequently.

Table 1. Clinical Data on 598 Patients Undergoing Thoracic Operation for Lung Cancer

Variable	1975–1982	1983–1989
No. of patients	290	308
Male/female ratio	20.1	6.0[a]
Age (y)		
Mean	61.5	65.5
Maximum	81	88
History of angina	33	41
Previous myocardial infarction	25	32
Congestive heart failure	18	15
Arterial hypertension	34	43
Ischemic changes on ECG	39	41
Positive exercise testing (n = 557)	31/270	31/257
Predicted FEV$_1$ after operation ≤1 L (n = 593)	21	46[b]
Patients undergoing pneumonectomy	103	97

[a] Significance: $p < 0.05$. [b] Significance: $p < 0.01$.

ECG = electrocardiogram; FEV$_1$ = forced expiratory volume in 1 second.

Table 2. Cardiac Complications in Patients Undergoing Thoracic Operation for Lung Cancer

	No. of Patients		
Cardiac Event	1975–1982	1983–1989	Total
Atrial arrhythmia	41	53	94
Transient myocardial ischemia	12	11	23
Myocardial infarction	3[a]	4[b]	7
Pulmonary edema	2	2	4
Cardiac arrest	1	1	2

[a] One of these patients died. [b] Three of these patients died.

The χ^2 test was used for statistical analysis. The limit of significance was set at a p value of less than 0.05.

Results

The occurrence of cardiac complications (Table 2) and of hospital mortality (Table 3) were similar during both study periods. Atrial tachyarrhythmias occurred in 94 (16%) of the 598 patients after operation (see Table 2). Atrial fibrillation was the most common dysrhythmia (87%), followed by supraventricular tachycardia and atrial flutter. No episodes of ventricular tachycardia were documented. Recurrent or persistent arrhythmias were documented in 18 (34%) of the 53 patients in the latter group (1983 through 1989) in whom arrhythmias developed. In 3

Table 3. Causes of 30-Day Operative Deaths[a]

	No. of Deaths		
Cause	1975–1982	1983–1989	Total
Bronchopneumonia	4	4	8
Myocardial infarction	1	3	4
Rupture of pulmonary artery	2	1	3
Pulmonary embolism	1	1	2
Cardiac arrest	1	0	1
Cerebral infarction	0	1	1
Gastrointestinal bleeding	1	0	1
Total	10 (3.4)	10 (3.2)	20 (3.3)

[a] Numbers in parentheses are percentages.

of them, persistent atrial fibrillation was associated with death from bronchopneumonia. Eighty percent of the arrhythmias occurred during the first 3 postoperative days, with a peak incidence (47%) on the second day after operation (Fig 1).

A similar distribution was shown in the occurrence of cardiac ischemic events. Postoperative myocardial ischemia was documented in 30 patients (5%), 23 of whom had transient ischemia and 7, myocardial infarction. Four (57%) of the myocardial infarctions were fatal.

An abnormal exercise test result and intraoperative hypotension were predictors of both types of cardiac complication ($p < 0.01$) (Table 4). A significant relation ($p < 0.01$) between postoperative atrial arrhythmias and pneumonectomy, preoperative ischemic changes on the ECG, and cardiac enlargement was observed, and a weaker association ($p < 0.05$) between postoperative atrial arrhythmias and age 70 years old or more, old (>6 months) myocardial infarction, arterial hypertension, and congestive heart failure. No relation was found between the occurrence of postoperative atrial arrhythmias and a history of angina or calculated postoperative pulmonary function. A significant association between a history of angina or old myocardial infarction and the incidence of transient ischemia postoperatively, but not myocardial infarction, was observed, whereas no association could be documented between myocardial ischemic events and preoperative findings of arterial hypertension, congestive heart failure, abnormal ECG, or extent of operation.

Twenty-three percent of the postoperative arrhythmias resolved spontaneously, 60% were treated with digitalis and quinidine sulfate, and 13% were initially treated with electrical countershock. Eighteen percent of the patients having no postoperative cardiac arrhythmias had received preoperative treatment with either digitalis or other antiarrhythmic drugs, as compared with 23% of the patients in whom dysrhythmias developed, a difference that is not significant.

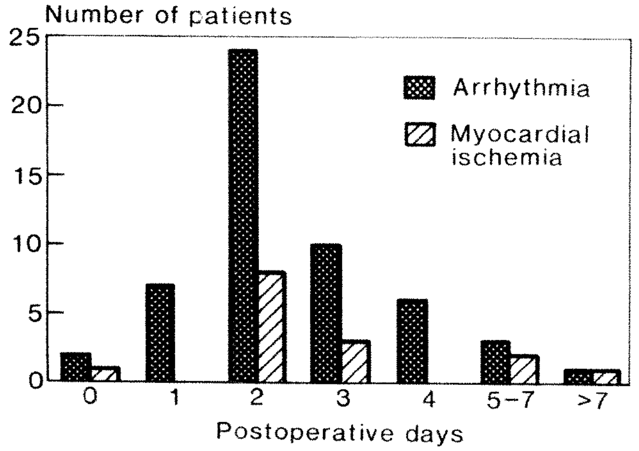

Fig 1. Distribution of postoperative cardiac events in 53 patients by days after operation.

Table 4. Relation of Preoperative and Intraoperative Factors to Postoperative Cardiac Events

Variable	No. of Patients	Patients With Cardiac Events: Arrhythmia	Patients With Cardiac Events: Ischemia
Age			
≥70 y	113	27[a]	8
<70 y	485	67	22
History of angina			
Yes	74	18	13[b]
No	524	76	17
Old myocardial infarction (>6 mo)			
Yes	57	15[a]	7[a]
No	541	79	23
Congestive heart failure			
Yes	33	10[a]	3
No	565	84	27
Arterial hypertension			
Yes	77	20[a]	7
No	521	74	23
Ischemic changes on ECG			
Yes	70	20[b]	7
No	528	74	23
Ischemic response to exercise testing			
Yes	62	21[b]	10[b]
No	495	68	16
Predicted FEV_1 after operation			
≤1 L	67	8	9[b]
>1 L	526	86	21
Operative procedure			
Pneumonectomy	200	46[b]	8
Other	398	48	22
Intraoperative hypotension			
Yes	49	19[b]	12[b]
No	549	75	18

[a] Significance: $p < 0.05$. [b] Significance: $p < 0.01$.

ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second.

The operative mortality rate was 3.3% (20 patients) (see Table 3). Four deaths (0.67%) were caused by myocardial infarction, 8 (1.3%) by bronchopneumonia, 3 by cardiopulmonary or cerebrovascular causes, 3 by intraoperative bleeding, and 1 by late gastrointestinal bleeding.

Patients who had undergone pneumonectomy had a significantly higher mortality rate than patients with less surgical intervention (6.5% versus 1.7%, $p < 0.01$). There was no increased mortality rate among patients in whom single episodes of arrhythmias developed as compared with those who remained in sinus rhythm (4% versus 3%). However, 3 (17%) of the 18 patients with persistent arrhythmia died. Compared with the mortality rate among patients without arrhythmias (2.4%), the difference was significant ($p < 0.01$).

Comment

In this retrospective analysis of patients undergoing thoracic surgical intervention for lung cancer, a very constant rate and distribution of atrial arrhythmias, myocardial ischemic events, and operative mortality were recorded during two subsequent 8-year and 7-year periods. In the latter period, more patients with highly restricted lung function underwent operation. However, more information concerning preoperative evaluation of cardiac risk was then available [9], and routine perioperative monitoring and management were also improved.

Compared with other studies, we noted very similar incidences of postoperative arrhythmias. Hence, the 16% rate of atrial tachyarrhythmias in all of our patients and the 23% rate in patients after pneumonectomy are consistent with the almost identical numbers in more recent studies [4, 5, 10] as well as with those in some earlier studies [3, 11, 12]. We found an increased rate of dysrhythmias after pneumonectomy compared with lobectomy. This was also noted in one earlier study [11], but not in another [3].

The peak incidence of arrhythmias and ischemic events on the second day after operation, with more than 80% of events occurring during the first 3 postoperative days, is consistent with the findings of a previous study [3]. A similar distribution by days was found for the occurrence of postoperative myocardial infarction [9].

The 30-day mortality rate of 3.3% for all our patients and of 6.5% for patients who had pneumonectomy are consistent with the reported 2% mortality rate after all forms of lung resection [7] and the 7% to 11% rate [4, 5, 13, 14] after pneumonectomy. As observed in other studies [11, 15], we found a significantly increased mortality among patients with persistent or recurrent arrhythmias compared with those without arrhythmias ($p < 0.01$). However, there was no increased mortality among patients with single episodes of dysrhythmias. Previous cardiac disease was clearly related to postoperative death. Hence, in 5 (71%) of 7 deaths where a cardiac complication was either the primary or a contributing cause of death, preoperative cardiac risk factors were revealed.

In agreement with some other studies [4, 12], we did not observe any ventricular arrhythmias. Many of our patients were followed up by continuous electrocardiographic monitoring for 2 to 3 days after operation, which to some degree increased the incidence of otherwise asymptomatic arrhythmias. Similarly, using daily routine ECG for a week postoperatively, Ghosh and Pakrashi [12] disclosed a 34% incidence of arrhythmias after a thoracic operation. However, with ambulatory electrocardiographic (Holter) monitoring, a high incidence (33%) of ventricular arrhythmias has been noted after thoracic operations, as has a higher incidence of atrial arrhythmias than observed in our study and previous studies [16].

The identification of reliable predictors of arrhythmias after thoracic operations would help us to develop preventive strategies. Hitherto most studies in this field have focused attention on general factors such as extent of operative procedure, grading of tumor growth, and preoperative pulmonary function, though some [5, 8] have extended the range by including the criteria of Goldman and colleagues [6] and by adding a modified exercise test [8]. Corroborating findings in other studies [4, 10], our study found that pulmonary function was not related to mortality or to occurrence of postoperative dysrhythmias in our patients, whereas significantly more ischemic events were recorded among patients with a predicted forced expiratory volume in 1 second of 1 L or lower. The latter finding was unexpected, as pulmonary function tests have not generally been regarded as useful variables to predict postoperative cardiac and hemodynamic abnormalities [10]. We found a weak association between old age and occurrence of arrhythmias, although in some studies [5, 6, 8], no such association was observed. However, in other studies [2, 7, 12], a connection between old age and postoperative complications was observed.

Very little is known about the importance of perioperative hemodynamics on the occurrence of postoperative arrhythmias. We found that intraoperative hypotension significantly increased the risk of both arrhythmias and myocardial ischemia. The importance of prolonged intraoperative hypotension as a predictor of postoperative myocardial infarction has repeatedly been stressed [6, 9, 17, 18]. Recently it was observed that surgical manipulation around the pericardium and lung hilum during thoracotomy could cause hypotension and transient atrial arrhythmia in 40% to 60% of the patients studied [19]. Hence, there is a possible link between hypotension and atrial arrhythmia.

An ischemic response to exercise testing was also found to be a significant predictor of both types of cardiac events. Similarly, in a recent study [8] involving geriatric patients undergoing thoracoabdominal operations, as well as in our previous study [20] involving patients undergoing peripheral vascular operations, a modified low-grade exercise test was of significant value in predicting the risk of postoperative cardiac complications.

Preoperative ischemic changes on the resting ECG were predictive of dysrhythmias but not myocardial ischemia. On the contrary, in patients with coronary heart disease, preoperative ST segment and T wave changes on the ECG were significantly related to postoperative repeat myocardial infarction or transient ischemia [9]. However, another study [6] did not report any predictive value of such ECG changes.

In patients with evidence of a previous old myocardial infarction (>6 months), a weak correlation to both arrhythmias and transient myocardial ischemia but not to repeat infarction was observed. In an earlier prospective study [9], there was a high incidence of postoperative repeat infarctions among such patients, whereas in other studies [6, 21], no such relation was demonstrated. A history of angina has been a controversial predictor in patients undergoing noncardiac surgical procedures. We found that angina correlated to an increased incidence of postoperative transient myocardial ischemia, but not to myocardial infarction or dysrhythmia. Similarly, based on results of our own previous study [9] as well as those of others [6, 17, 22], there is no support for stable angina as a predictor of repeat myocardial infarction after major thoracoabdominal operations.

Detection of silent myocardial ischemia, comprising 75% to 90% of total diurnal ischemic episodes, preoperatively and perioperatively by Holter monitoring bears a highly significant correlation to adverse cardiac outcomes after vascular operations [22, 23]. However, we are aware of no reports that evaluate myocardial ischemia by Holter monitoring for thoracic operations.

There are no generally accepted causes of arrhythmias after thoracic surgical procedures. After thoracotomy, pulmonary physiology and oxygenation are severely impaired, particularly on the first and second postoperative days, independent of the extent of operation [24]. In the present study and in our recent placebo-controlled study [24] in which we demonstrated a considerable right ventricular strain caused by hypoxic pulmonary vasoconstriction in the remainder of the lungs, the cardiac arrhythmias peaked on the second postoperative day. Right ventricular strain was associated with a high incidence of atrial tachyarrhythmias, which could be prevented by a regimen of oxygen therapy and oral administration of verapamil hydrochloride, a calcium-channel blocker with pulmonary vasodilating properties, continued for 2 days after operation. Verapamil also abolished ischemic changes in the ECG. Oral verapamil seemed to be beneficial for the imbalance between the strained right and hypodynamic left ventricles. In the present study, congestive heart failure and cardiac enlargement in particular predicted arrhythmias. Hence, an already enlarged heart would be more prone to develop arrhythmias by this mechanism. In addition, the results suggest that intraoperative hypotension causing myocardial ischemia would also elicit arrhythmias.

There are no generally accepted preventive regimens for these arrhythmias. Digoxin has been the only extensively studied drug to prevent atrial arrhythmias after thoracic operations. However, because of positive [25] as well as negative [26] reported results, this regimen remains controversial. Recently it was demonstrated that intravenous infusion of the antiarrhythmic drug flecainide acetate for 3 days after thoracotomy prevented or reduced atrial and ventricular arrhythmias without any side effects [16]. The preventive effect of verapamil in our previous study [24] also seems promising. Verapamil also could prevent ischemic episodes after thoracotomy [24], whereas the effect of β-blockers is unknown in this respect. In the present study, previous medication with β-blockers was continued in patients with verified coronary heart disease, but preoperative treatment with these drugs was not started because of an ischemic response to the exercise test only.

In conclusion, despite improvements in anesthetic and monitoring techniques in the last decade, the incidence of cardiac arrhythmias after thoracotomy has not decreased. As these seem to be associated with an increased mortality and morbidity, we need to develop better preventive strategies. Exercise testing remains the best predictor of postoperative ischemic and arrhythmic cardiac events. Holter monitoring would be valuable to identify patients who need a preventive cardiac drug regimen. Intraoperative hemodynamics should be kept as stable as possible, and overhydration should be avoided.

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Salvage Transvenous Rapid Atrial Pacing to Terminate Atrial Flutter After Cardiac Operations

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Atrial flutter occurring after cardiac operations normally responds well to atrial overdrive pacing through epicardial atrial pacing wires and medication. When this fails, transvenous atrial overpacing offers an attractive alternative. We performed the procedure 29 times in 25 patients. Sinus rhythm returned acutely after 25 procedures in 21 patients and persisted with medication in 20 patients at follow-up. The procedure was well tolerated by all.

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Atrial fibrillation and atrial flutter occur in 5% to 40% of patients after coronary artery bypass grafting [1] and in many patients after heart valve replacement. Prophylaxis with β blockers has been found to be only partially effective, although more so than digoxin or verapamil hydrochloride [1]. Intraoperative placement of epicardial atrial pacing wires has been advocated to facilitate diagnosis and termination of the arrhythmia [2] and is applied in all patients undergoing cardiac operations at our institution. These wires are frequently used diagnostically or therapeutically for atrial flutter.

This report concerns all patients at our institution in whom atrial flutter developed after a cardiac operation from January 1985 through February 1991 who did not respond to medical treatment and in whom rapid termination was considered desirable, but the epicardial wires were either nonfunctional or had already been removed. Synchronized cardioversion is not performed at our institution for this indication.

Material and Methods

The study group consisted of 25 patients (23 men and 2 women) aged 61.8 ± 7.0 years (range, 51 to 72 years). Twenty-two underwent coronary artery bypass grafting, 2 had aortic valve replacement, and 1 underwent the combined procedure. Patients without functional atrial wires were selected for transvenous atrial overpacing if, in spite of medication with digoxin plus verapamil (80 mg three to four times daily) or β blockers (metoprolol tartrate, 50 mg two to three times daily), amiodarone hydrochloride (800 mg daily), or a combination of these, atrial flutter with rapid ventricular response had persisted for several days or was poorly tolerated. If transthoracic epicardial atrial wires were present and functioning, they were used routinely as described elsewhere [3]. Transvenous overpacing was not performed in any patient after mitral valve replacement because persistent sinus rhythm was considered unlikely. During the same period, more than 4,700 cardiac operations were performed at our institution.

All patients gave informed consent. They were not kept fasting, but the procedure was delayed for several hours after the main meal. No antibiotic prophylaxis was given. Oral anticoagulation, which 4 patients were receiving, was not withdrawn. No medical antiarrhythmic pretreatment other than that already being given was provided at the time of overpacing.

Venous access under local anesthesia was through the internal jugular or subclavian vein (usually on the right side) using a bipolar J wire (model 370-420; Cordis, Roden, the Netherlands) in 23 patients and through the femoral vein using a ventricular bipolar electrode (Cordis model 370-230) in the other 2. Successful positioning without fluoroscopy was attained by searching for the largest endocavitary p-wave in 21 of the patients. In 4, fluoroscopy was needed for correct positioning.

In all procedures, rapid atrial stimulation was accomplished using either a Philips TP 300 or a Medtronic 5320 stimulator. Pacing was begun at a rate just above that of the flutter rate and increased by 10 to 20 beats/min until atrial entrainment was confirmed. Pacing was stopped abruptly, and if atrial flutter persisted, the procedure was repeated until a rate of about 20 beats/min higher than that of the previous attempt was reached. An output of 20 mA was used in all attempts.

Results

Twenty-two patients underwent the procedure once, 2 had it twice, and 1, three times because of recurrences. Thus, a total of 29 procedures were performed. Transvenous overpacing was performed for the first time 16.0 ± 17.5 days (range, 4 to 78 days) after operation. Second pacing procedures were done 7, 15, and 72 days postoperatively. These 3 patients were the only ones with recurrences of atrial flutter. The lone third procedure took place on the 134th postoperative day.

Twenty-three patients, of whom 12 had nonfunctioning epicardial atrial pacing wires and 11 had had the wires removed, were still in the hospital for the first procedure. The other 2 patients were treated as outpatients. The 2 patients who underwent aortic valve replacement had development of complete atrioventricular block postoperatively. They had overpacing of atrial flutter from the

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femoral vein so as not to dislodge the implanted atrial and ventricular pacing leads.

Sinus rhythm was attained with 25 procedures in 21 patients. It was maintained with a regimen of digoxin plus verapamil or β blockers at unaltered doses in 20 patients at a follow-up of 1.5 to 65 months after the last rapid atrial pacing. Amiodarone administration was discontinued at a maximum of 4 weeks after conversion to sinus rhythm in all 5 patients who were taking it. The 2 patients in complete atrioventricular block received no antiarrhythmic drugs either before or after the procedure. In 4 patients, all with severe left ventricular dysfunction, atrial fibrillation and not sinus rhythm was obtained, and it persisted during follow-up. The ventricular rate was controlled more easily in all 4 than it had been during atrial flutter. Thus, no patient remained in atrial flutter after transvenous atrial overpacing.

Of the 3 patients undergoing multiple overpacing procedures, 2 were in sinus rhythm at a follow-up of 17 and 31 months, and the third was in permanent atrial fibrillation. Of 6 patients who underwent the procedure more than 21 days postoperatively, 3 remained in sinus rhythm and 3 were in atrial fibrillation at last follow-up.

Aside from asymptomatic inhibition of an implanted pacemaker for several seconds during rapid atrial stimulation in 1 patient, there were no complications resulting from the procedure. The pacing wire was removed immediately after the procedure and the venous sheath, within 2 hours in all patients.

Comment

Rapid atrial pacing using transthoracic epicardial atrial wires to terminate atrial flutter after cardiac operations has been performed for two decades [4]. It is a routine procedure for us and is successful in the great majority of patients with postoperative atrial flutter. Transvenous rapid atrial pacing has also been described [5], but it is invasive and should be avoided when epicardial pacing or medical conversion is possible. Prevention of atrial tachyarrhythmias with β blockers, for example, is only partially successful [1], and, as in 12 of our patients, pacing thresholds of epicardial pacing wires often rise rapidly, thus precluding noninvasive overpacing. In addition, as in our 13 other patients, atrial flutter can occur after pacing wires have been removed.

Possible alternative strategies to transvenous atrial overpacing are continued medical treatment, transesophageal rapid atrial pacing, and synchronized cardioversion. The first is not uniformly effective; most of our patients had been treated medically for several days. Transesophageal stimulation is no less invasive, and synchronized cardioversion requires general anesthesia.

The fact that 3 of our patients requested a second or third transvenous overpacing procedure, and the persistent sinus rhythm in a high percentage of patients, indicate good acceptance of the procedure in this small subgroup of patients. This procedure, which should be performed by a physician with the necessary experience, should be considered for any patient with atrial flutter after a cardiac surgical procedure who does not respond to medical treatment and in whom epicardial pacing wires are no longer functioning or have been removed.

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Fresh Blood Units Contain Large Potent Platelets That Improve Hemostasis After Open Heart Operations

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Twenty units of fresh whole blood were separated into fresh packed red blood cells (PC) and platelet-rich plasma (PRP) and were transfused to 40 patients immediately after coronary bypass grafting. Patients were preoperatively randomized to receive either PRP (group A, 20 patients) or PC (group B, 20 patients). Platelet number in the PRP group was greater, but not significantly greater, than in the PC group (7.5 ± 3 versus 5.9 ± 2.2 × 10^{10}; p = not significant). However, mean platelet volume in the PC group was significantly greater (8.75 ± 1.1 versus 6 ± 0.7 fL). Postoperatively, group A patients bled more than group B (566 ± 164 versus 327 ± 41 mL; $p < 0.01$) and received more red blood cell units (2.7 ± 1.2 versus 1.6 ± 0.7 U; $p < 0.05$) and a larger number of blood products (5.9 ± 3.7 versus 2.6 ± 1.2 U; $p < 0.05$). Transfusion of PRP to group A increased platelet count from 128 ± 20 to 148 ± 110 × 10^9/L; however, platelet functions did not improve. Administration of PC to group B increased platelet count from 139 ± 22 to 156 ± 23 × 10^9/L, improved platelet aggregation (with collagen from 33% ± 20% to 53% ± 23%, with epinephrine from 36% ± 24% to 51% ± 20%; $p < 0.05$), and corrected the prolonged bleeding time. The results suggest that the improved hemostasis observed after fresh whole blood administration is related to the large, potent platelets that remained in the PC and were not separated to the PRP during standard platelet concentrate preparation.

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We [1, 2] have recently shown that when compared with platelet concentrates, fresh whole blood (FWB) has a superior effect on recovery of platelet function after open heart operations. We [3, 4] have also shown that the larger platelets, which are known to be more potent [5–11], play a major role in hemostasis after open heart procedures.

If platelets are, indeed, the determinant of quality of hemostasis after open heart operations, why then are the platelets contained in FWB more effective than those of platelet concentrates? It was our assumption that the larger and more potent platelets are sedimented together with the packed cell fraction during the centrifugation for separation of the platelet concentrate. The present study was designed to evaluate this assumption and its clinical manifestations after open heart operations.

Patients and Methods

Forty patients (30 men and 10 women) who underwent coronary bypass grafting were randomized before operation into two groups. Group A (20 patients) received immediately after cardiopulmonary bypass platelet-rich plasma (PRP), which had been separated from FWB after donation on the morning of the operation and was kept at room temperature (20° to 24°C) until transfusion. The remaining 20 patients (group B) received fresh packed red blood cells (PC) after removal of PRP. Separation of FWB into PRP and PC was done by conventional centrifugation for 3 minutes at 1,740 *g* [12] (Sorvall RC-3 Dupont/Sorvall Inc, Newton, CT). Platelet count and volume were measured and compared in the PC and PRP. Platelet count was determined by electronically thresholding a selective size range of blood particles from 2 to 20 μm^3. The particles entering the sensing zone cause an impedance change between two silver-silver chloride electrodes that is proportionate to the size of the particle. The particles were counted according to the Coulter system [13]. Mean platelet volume (MPV) was derived by computing the arithmetic mean volume from the fitted platelet distribution curve. The result was expressed in femtoliters. The S-plus analyzer calculates plateletcrit by multiplying platelet count by MPV. Total platelet volume was calculated by multiplying plateletcrit by the volume of the respective blood component unit (PC or PRP).

Each FWB unit was cross-matched and tested for hepatitis B surface antigen, antibody, and human immunodeficiency virus before administration. Whenever possible, potential donors were tested several days before donation.

Patients who had been taking dipyridamole or aspirin-containing drugs during the 2 weeks preceding their operation were excluded from the study.

All patients were rewarmed to 35°C before discontinuation of cardiopulmonary bypass. Reversal of the heparin

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effect by protamine was monitored by the activated clotting time [14]. All pump blood was returned to the patient (through the aortic cannula or intravenously via infusion bags). The following postoperative hematological variables were studied in all patients: Bleeding time, platelet count, MPV, and platelet aggregation in response to collagen, adenosine diphosphate, and epinephrine. All assays were done after protamine administration and repeated after transfusion of PRP or PC to groups A and B, respectively.

Platelet aggregations were determined by the method of Born and Cross [15] on a PAP-4 aggregometer (BIO/DATA Corporation, Hatboro, PA). The aggregation agents were adenosine diphosphate (final concentration, 3 μmol/L), collagen (Ethicon Inc, Somerville, NJ; final concentration, 0.02 mg/mL), epinephrine (1 μg/mL), and ristocetin (1.2 mg/mL). All aggregations were performed on PRP with a platelet count higher than 190 × 10^9/L, Platelet-rich plasma was prepared by centrifuging citrated blood (3.2%) at 800 *g* for 10 minutes. The normal slope of aggregation was 45 degrees or higher. Normal aggregation amplitude averaged 60% to 90%, and it was determined in our laboratory on 50 normal control subjects.

The number of blood units transfused, the total number of blood products (red blood cells, plasma and platelet concentrates) transfused, and the total volume of chest tube drainage in the initial 24 hours after patients arrived in the intensive care unit were recorded by the intensive care unit personnel for evaluation of clinical hemostasis. For calculation of blood components transfused to every patient, 1 U of blood was added to the final number of red blood cells transfused in group B, and 1 U of blood products to the final number of blood products in both groups to account for the PC and PRP transfused in the operating room to groups B and A, respectively.

The policy of blood transfusion in the intensive care unit differed in the immediate and late postoperative periods. Most blood transfusions were given in the first 8 postoperative hours. The indications for blood transfusion were hemodynamic variables, such as low systemic and left atrial pressures, and constricted periphery. The amount transfused depended strongly on the amount of blood lost through the chest tubes. Once the patient's condition was stabilized completely, the indication for further blood transfusion was a hemoglobin level lower than 10 g/100 mL. Platelet concentrate transfusions were administered only to patients with active bleeding if the platelet count was less than 100 × 10^9/L.

All results were expressed as mean ± standard deviation. Paired and nonpaired Student's *t* tests were used for statistical analysis.

Results

The two groups were similar in age, sex, bypass time, and lowest body temperature (Table 1). There were also no significant differences between the two groups in preoperative and postoperative bleeding time, platelet count, plateletcrit, and platelet function (Tables 1, 2).

The average platelet number in the whole blood units was 1.1 ± 0.3 × 10^{11}. The average number of platelets in the PRP was higher than in the PC (7.5 ± 3 versus 5.9 ± 2.2 × 10^{10}, respectively). However, the difference did not reach statistical significance (Fig 1).

Table 1. Patient Characteristics

Variable	Group A, PRP (20 patients)	Group B, PC (20 patients)
Age (y)	60 ± 6.3	58 ± 7.2
Sex (M/F)	16/4	14/6
Redo CABG	1	2
BSA (m^2)	1.77 ± 0.18	1.70 ± 0.16
Bypass time (min)	138 ± 11	124 ± 14
Aortic cross-clamp time (min)	55 ± 6	51 ± 5
Lowest body temp	26.4 ± 1.2	25.7 ± 1.4
Preop PLT count (×10^9/L)	227 ± 18	231 ± 15
Preop PCT	0.166 ± 0.096	0.185 ± 0.105
Aggregation (%)		
Collagen	62 ± 25	63 ± 22
ADP	72 ± 8	67 ± 24
Epinephrine	64 ± 24	73 ± 15
Ristocetin	76 ± 9	70 ± 20
Preop bleeding time (min)	3.2 ± 0.6	3.1 ± 0.4

ADP = adenosine diphosphate; BSA = body surface area; CABG = coronary artery bypass grafting; PC = fresh red blood cells; PLT = platelet; PRP = platelet-rich plasma.

Mean platelet volume in the PC fraction was significantly larger than in PRP (8.75 ± 1.1 versus 6 ± 0.7 fL; $p < 0.001$) (Figs 1, 2). Moreover, in each individual unit, without exception, the MPV in the PC was larger than in the PRP (see Fig 2). The calculated total platelet volume (plateletcrit × volume of fraction unit) was similar in the PC and PRP (53 ± 19 versus 52.5 ± 25 mL; p = not significant).

Intravenous administration of PC improved platelet aggregation and corrected the prolonged bleeding time significantly better than PRP. Platelet counts increased similarly in both groups (group A, 20 ± 9 × 10^9; group B, 17 ± 8 × 10^9) (see Table 2).

Twenty-four-hour blood loss was significantly lower in group B (327 ± 41 versus 566 ± 164; $p < 0.01$). The total volume of blood transfused and the amount of blood products transfused (ie, number of platelet concentrates, plasma, and red blood cell units) were significantly higher in group A (2.7 ± 1.2 versus 1.6 ± 0.7 U and 5.9 ± 3.7 versus 2.6 ± 1.2 U, respectively; $p < 0.05$) (see Table 2). Only 1 patient in group B required transfusion of platelet concentrates during the first 24 postoperative hours compared with 5 patients in group A. The reduced exposure to donors of blood products in group B is mainly due to the lower number of platelet concentrates transfused (see Table 2).

One patient in group B had to be returned to the operating room because of excessive mediastinal bleeding (400 mL during the first hour in the intensive care unit); however, a surgical source of bleeding was found, and the patient was not excluded from the study.

Table 2. Effect of Fresh PRP versus Fresh PC Transfusion on Hemostasis After Cardiopulmonary Bypass

	Group A (PRP)		Group B (PC)	
Variable	Post-operative	Post-transfusion	Post-operative	Post-transfusion
PLT count ($\times 10^9$/L)	128 ± 20	148 ± 17	139 ± 22	156 ± 23
PCT	0.107 ± 0.060	0.120 ± 0.070	0.116 ± 0.060	0.130 ± 0.06
Bleeding time (min)	7.6 ± 1.7	7.3 ± 1.8[a]	7.2 ± 1.2	4.6 ± 1.6
Aggregation (%)				
Collagen	37 ± 20	34 ± 16[a]	33 ± 20	53 ± 23
ADP	58 ± 26	54 ± 27	60 ± 15	62 ± 19
Epinephrine	43 ± 19	28 ± 12[a]	36 ± 24	51 ± 20
Ristocetin	86 ± 20	78 ± 21	73 ± 22	77 ± 13
24-hour blood loss (mL)		566 ± 164[b]		327 ± 41
RBC requirement (U)		2.7 ± 1.2[a]		1.6 ± 0.7
PLT concentrate transfusion (U)		2.8 ± 4		0.5 ± 2.2
Total blood product consumption (U)		5.9 ± 3.7[a]		2.6 ± 1.2

[a] $p < 0.05$, A versus B. [b] $p < 0.01$, A versus B.

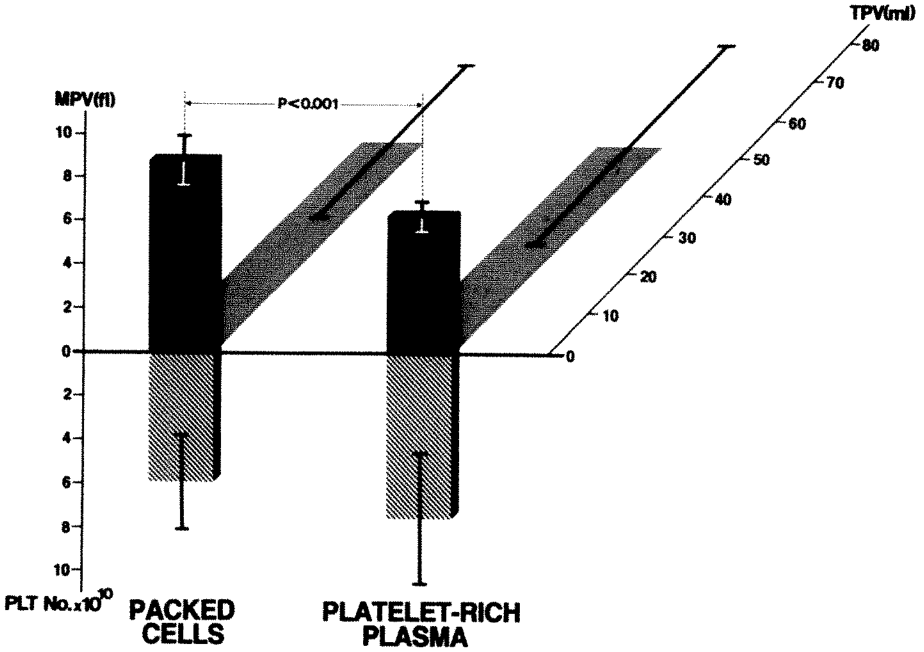
ADP = adenosine diphosphate; PC = fresh red blood cells; PCT = plateletcrit; PLT = platelet; PRP = platelet-rich plasma; RBC = red blood cell.

Comment

The present study was designed in an attempt to solve the enigma why transfusion of fresh whole blood at the termination of cardiopulmonary bypass improves hemostasis better than transfusion of platelet concentrates [1, 2, 16]. The key word for solving this enigma is "large platelets." Large platelets are more potent and hemostatically superior to smaller platelets [5–11]. During preparation of platelet concentrates, fresh blood is separated into PC and PRP. The large platelets are sedimented during centrifugation together with the packed red blood cell fraction and are not included in the PRP, which is later used for preparation of platelet concentrates. One can arrive at this conclusion on the basis of the significantly higher MPV in the PC compared with PRP (see Fig 2), particularly when comparing each of the 20 separated units, where MPV in the PC was larger than in PRP *with no exception.*

The observation that large platelets are metabolically and functionally more active than the small platelets is not new. Large platelets have been found to contain more glycogen adenine nucleotides, orthophosphate, and reduced forms of gluthathione, nicotinamide adenine dinucleotide, and nicotinamide adenine dinucleotide phos-

Fig 1. Comparison of platelet (PLT) number, mean platelet volume (MPV), and total platelet volume (TPV) in the fresh red blood cells and platelet-rich plasma.



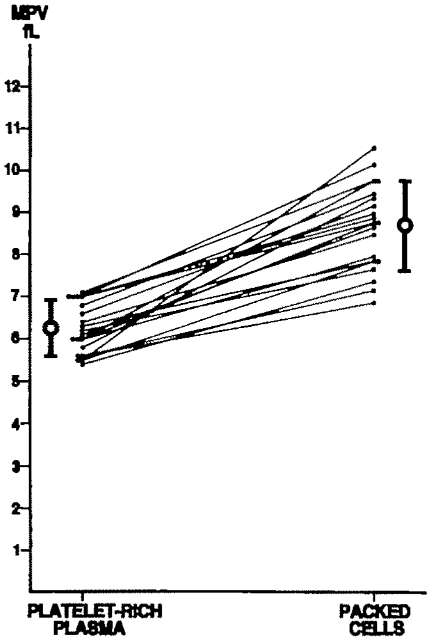


Fig 2. Individual comparison of mean platelet volume (MPV) *in the fresh red blood cells and platelet-rich plasma.*

phate [5–7]. They show greater rate of metabolism of protein [8, 9], carbohydrate [7], and lipid metabolism [10]. Large platelets aggregate better in response to adenosine diphosphate, epinephrine, thrombin, and collagen [5, 6] and respond to lower concentrations of adenosine diphosphate [17]. They show greater adhesiveness to glass beads and collagen [18] and are less susceptible to inhibition by prostacyclin [11]. Clinical observations also indicated the hemostatic superiority of large platelets [19]. In patients with severe thrombocytopenia, MPV was found more important than platelet count for prediction of bleeding tendency [20]. A unit of FWB contains both the small platelets that are separated to the platelet concentrate and the large and potent platelets that are lost from platelet concentrate during separation of blood to PC and PRP. Therefore there is no doubt that FWB is hemostatically superior to stored platelet concentrate.

It must be emphasized that no attempt was made here to prove that fresh red blood cells restore hemostasis better than fresh platelet concentrate. The slightly lower postoperative bleeding and slightly higher need for blood transfusions in patients of group B, although statistically significant, does not bear real clinical significance. However, together with the better platelet aggregation and shorter bleeding time observed in this group, they serve as indicators of better hemostatic effect of PC compared with PRP. Those scientific observations of minor differences between the two groups are important, as they correspond to the "trapping" of the more potent large platelets within the fraction of the red blood cells.

Because this study was not conducted in a double-blind fashion, a biased attitude to postoperative blood transfusions might be suspected, provoking distortion of the postoperative clinical picture. However, management of patients in the intensive care unit was conducted by the intensive care unit personnel, who were neither involved in nor aware of ongoing studies. The decision to transfuse homologous blood or blood components was based entirely on the hemodynamic situation of the patient and blood loss in the first 6 to 8 postoperative hours.

In conclusion, this study demonstrates that the conventional blood bank method of blood separation is deficient in the sense that the larger and most potent platelets cannot be separated into the units of platelet concentrate.

It should be noted that in searching for donors for FWB, donors who are blood-related to the patient should be avoided. This is because of the very rare but fatal risk of graft-versus-host reaction caused by the donated lymphocytes [24].

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Clinical Application of Total Body Retrograde Perfusion to Operation for Aortic Dissection

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The use of profound hypothermia and total circulatory arrest in the surgical treatment of aortic dissection has previously been reported. However, the safe period of prolonged circulatory arrest with hypothermia remains controversial. We have developed a technique of hypothermic total body retrograde perfusion to achieve systemic organ protection: cerebral protection by continuous retrograde perfusion through the superior vena cava, myocardial protection by coronary sinus infusion, and abdominal visceral organ perfusion by continuous retrograde perfusion through the inferior vena cava. Our technique yields a relatively bloodless operating field and avoids hypoperfusion of vital organs through a false lumen.

(Ann Thorac Surg 1992;53:655–8)

The use of the "open" distal anastomosis technique has permitted satisfactory results of ascending aorta and aortic arch reconstruction [1]. This technique facilitates an appraisal of the underlying pathologic condition and the repair of an aortic dissection. The technique is, however, performed under circulatory arrest. The optimal level of hypothermia and its effectiveness in achieving cerebral and visceral protection during circulatory arrest in humans are unknown. We have used a method of hypothermic total body retrograde perfusion composed of continuous retrograde cerebral perfusion through the superior vena cava with cerebral protective drugs [2–5], retrograde coronary sinus infusion (multidose cold blood cardioplegia), and continuous retrograde abdominal visceral organ perfusion through the inferior vena cava, thereby achieving cerebral, myocardial, and visceral protection.

Material and Methods

Five consecutive patients operated on for aortic dissection (Stanford type A) from September 1990 to January 1991 were included in this study (Table 1). One patient had a traumatic aortic pseudoaneurysm, 1 underwent a modified Bentall operation using a Dacron graft with a St. Jude Medical valve, and 1 underwent reoperation on an aortic dissection because of a new tear near the distal anastomosis. Informed consent to our procedure was obtained from each patient. Our technique is detailed in Figure 1.

All cases were approached through a median sternotomy with cannulation of the common femoral artery and bicaval cannulation through the right atrium. Extracorporeal circulation was established with a flow rate of 2.5 to 2.8 $L \cdot min^{-1} \cdot m^{-2}$ using membrane oxygenation and a heat exchanger. Core cooling was started at the onset of cardiopulmonary bypass and continued until a rectal temperature of 20°C or less was reached. The patient's temperature rapidly fell and the heart fibrillated; at this point, the ascending aorta was clamped immediately proximal to the origin of the brachiocephalic artery. The right atrium was opened and a balloon catheter for retrograde myocardial protection was inserted into the coronary sinus. Infusion of cold blood cardioplegic solution was initiated, and the aortic wall was transected several centimeters above the coronary ostium. Cold blood cardioplegia was instilled every 20 minutes.

Both the aortic lumen and the aortic valve were carefully inspected whether intimal tears or valvular lesions existed or not. In our patients, intimal tear was not observed proximal to the aortic clamp. In 4 patients (excluding the patient undergoing a Bentall operation), a preclotted woven Dacron graft was sutured to the proximal aortic stump.

After the proximal aortic anastomosis was completed, the aortic clamp was released. Pump perfusion was then transiently discontinued at a rectal temperature of less than 20°C, and cerebral protective drugs (mannitol, 10 mL/kg; phenytoin, 10 mg/kg) were infused systemically. Next, total body retrograde perfusion was started. Venous drainage cannulas were switched over to the arterial return circuit, and oxygenated blood was retrogradely pumped through each vena cava. The returned flow from the total body was aspirated with a suction tube positioned in the aorta and collected into the venous reservoir of the extracorporeal circulation circuit. Perfusion flow rate in the superior and inferior venae cavae was maintained at 300 to 600 mL/min. The upper venous pressure was limited to 30 mm Hg. The ascending aorta

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Table 1. Results of Total Body Retrograde Perfusion for Aortic Dissection in 5 Patients

Patient No.	Age (y)	Weight (kg)	Type of Repair	Total CPB Time (min)	CPB-1 (min)	CPB-2 (min)	CPB-3 (min)	Rectal Temperature During Retrograde Perfusion (°C)
1	59	68	Replacement of ascending aorta	189	58	32	99	20.0
2	53	67	Replacement of ascending aorta (redo)	258	61	67	130	18.6
3	54	37	Modified Bentall operation	351	160	51	140	16.1
4	18	65	Replacement of ascending aorta & brachiocephalic artery	215	24	110	81	19.6
5	55	48	Replacement of ascending aorta	162	49	50	63	16.6

CPB = cardiopulmonary bypass; CPB-1 = interval from the start of cardiopulmonary bypass to total body retrograde perfusion through both venae cavae; CPB-2 = duration of total body retrograde perfusion through both venae cavae; CPB-3 = duration of bicaval drainage and perfusion through the tube graft for rewarming.

was incised longitudinally, and the pathologic condition of the interior of the transverse arch and origin of the arch vessel could be appraised. The intimal tear was located near the site where the aortic clamp was placed. The aortic segment or appropriate portions of aortic arch containing intimal tear were resected, and the peripheral end of the Dacron graft was secured to the distal aortic stump in the same fashion as done in the proximal stump.

After replacement of aorta was accomplished during total body retrograde perfusion under profound hypothermia, the patient was then warmed with cardiopulmonary bypass. To prevent retrograde perfusion of the false lumen, an arterial cannula was inserted into the tube graft for perfusion of oxygenated blood. Venous drainage through both venae cavae was resumed, and conventional cardiopulmonary bypass was reestablished. All air was carefully evacuated. Cardiopulmonary bypass was discontinued at 36°C, and hemostasis was achieved by administration of protamine sulfate, fresh whole blood, and fresh frozen plasma.

Results

The mean cardiopulmonary bypass time was 253 minutes (range, 189 to 351 minutes). The mean time from the start of cardiopulmonary bypass to total body retrograde perfusion was 70 minutes (range, 24 to 160 minutes). The mean time of total body retrograde perfusion was 82 minutes (range, 32 to 110 minutes). The mean lowest rectal temperature during total body retrograde perfusion was 19°C (range, 16° to 20°C). The postoperative course was uneventful in all 5 cases. There were no neurological complications, and no renal or hepatic dysfunction occurred. Postoperatively the blood urea nitrogen concentration peaked at 10.0 to 12.9 mmol/L (28 to 36 mg/dL), and the peak serum creatinine concentration level was

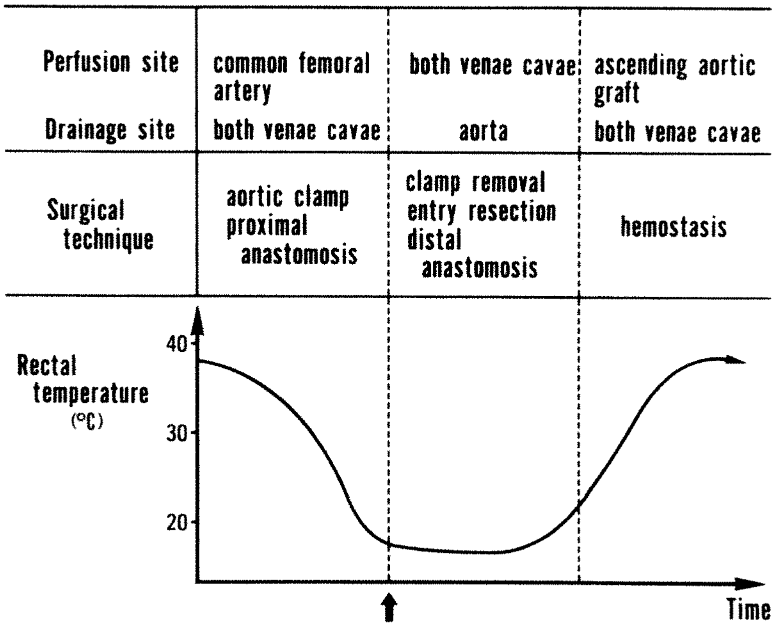

Fig 1. Schematic representation of operation for aortic dissection using the total body retrograde perfusion method. The perfusion site for oxygenated blood and the drainage site for systemic venous blood are displayed. The arrow *indicates the point of infusion of cerebral protective drugs.*

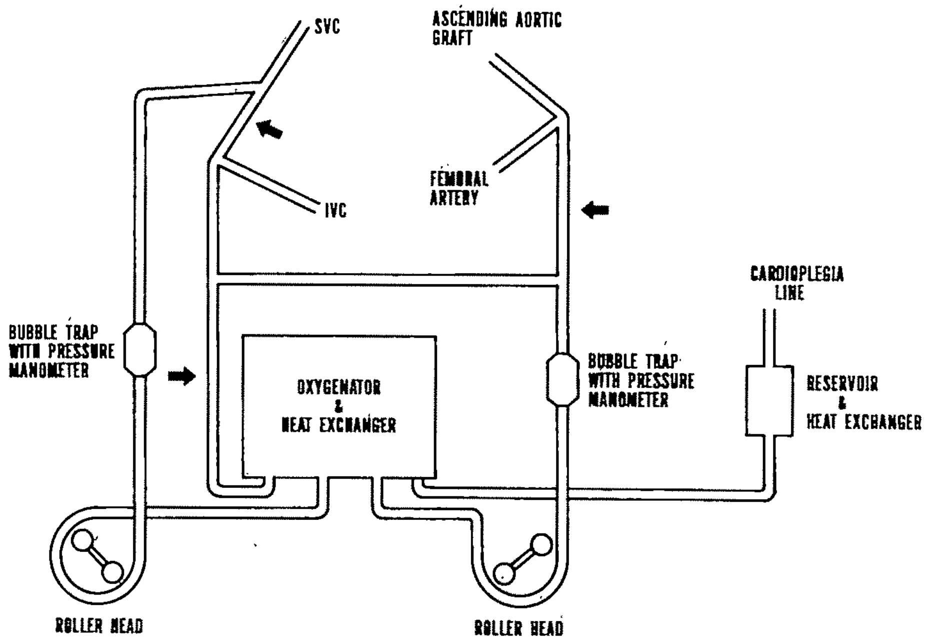
SVC
ASCENDING AORTIC GRAFT
IVC
FEMORAL ARTERY
CARDIOPLEGIA LINE
BUBBLE TRAP WITH PRESSURE MANOMETER
OXYGENATOR & HEAT EXCHANGER
BUBBLE TRAP WITH PRESSURE MANOMETER
RESERVOIR & HEAT EXCHANGER
ROLLER HEAD
ROLLER HEAD

Fig 2. A diagram of the extracorporeal circuit for total body retrograde perfusion is displayed. The arrowed *limbs are clamped, and oxygenated blood is perfused through both venae cavae.* (IVC = *inferior vena cava;* SVC = *superior vena cava.)*

132.6 to 159.1 μmol/L (1.5 to 1.8 mg/dL). Liver function was within normal limits, and the function of digestive organs was normal.

Comment

Aortic dissection and dissecting aneurysm are serious aortic diseases. Especially in Stanford type A dissection, death may occur suddenly or within a few hours or days after the onset without operation. To arrest progression of an aortic dissection, medical therapy must be instituted soon after the diagnosis is made. Extension of dissection should be prevented during operation as well. Usually, the common femoral artery is the preferred site of arterial cannulation during operation on aortic dissection. However, arterial perfusion through the common femoral artery may be through the true or false lumen, depending on the manner in which the dissection reenters [6]. Perfusion of the false lumen may cause intraoperative hypoperfusion of the hepatic, renal, or cerebral circulation. Extrinsic compression of the true lumen by the false lumen increases the risk of multiple organ system failure.

We developed a technique of continuous retrograde cerebral, renal, hepatic, and visceral organ perfusion through both venae cavae and myocardial perfusion through the coronary sinus during profound hypothermia. This method can provide cold oxygenated blood to the vital organs and avoid the complications of air emboli associated with circulatory arrest. The safety of retrograde perfusion through vena cava has been demonstrated. Retrograde perfusion through vena cava for a few minutes was employed for evacuation of air in systemic circulation during cardiopulmonary bypass, as first reported by Mills and Ochsner [2]. Lemole and colleagues [3] applied this maneuver to implanting an intraluminal sutureless graft for acute aortic dissection. Kusuhara and colleagues [4] employed intermittent retrograde cerebral perfusion through the superior vena cava under profound hypothermic circulatory arrest for surgical treatment of aortic arch aneurysm. Hendriks and colleagues [7] suggested that the retrograde perfusion through vena cava might maintain normal aerobicity of vital organs.

An "open" distal anastomosis during circulatory arrest simplifies the operative procedure, avoids clamp injury to the fragile dissected aortic tissue, and allows direct visualization of lesions involving the aortic arch and its tributaries. Cooley and Livesay [8] reported that it took less than 10 minutes to perform open distal anastomosis. However, aortic repair requires considerable surgical skill, and it might take a much longer time. The safe upper limits of continuous circulatory arrest during hypothermia in adults have not been firmly established. Our technique creates a relatively bloodless operating field and permits safe, complete repair of the aortic lesion without the fear of clamp injury. This maneuver can be performed with a simplified extracorporeal circulation circuit (Fig 2) as opposed to the selective cerebral perfusion method, which requires a separate pump.

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INVITED COMMENTARY

This is a most provocative report, providing documentation of adequate preservation of central nervous system function after interrupting antegrade cerebral perfusion for as long as 110 minutes. To the best of my knowledge this represents the longest reported interval of retrograde cerebral perfusion used in humans. At the very least this report indicates that long intervals of hypothermic retrograde cerebral perfusion are not in themselves injurious to the brain.

In our own experience, those patients with periods of retrograde perfusion of 32, 50, and 51 minutes would have been expected to have an excellent outcome if the circulation simply had been arrested at the temperature used by Yasuura and associates. However, the patients who had 67 and 110 minutes of hypothermic retrograde perfusion would almost certainly have had at least transient cerebral injury if circulatory arrest alone had been used for this period. Thus, Yasuura and associates' contention that the technique of hypothermic retrograde cerebral perfusion does provide preservation of cerebral function is not unreasonable. The mechanism of this protection is, however, uncertain. It could be that the retrograde perfusion merely provides better maintenance of low brain temperatures while antegrade perfusion is interrupted. It is also possible that the retrograde flow is simply preventing accumulation of hydrogen ion and other metabolites. Finally, and perhaps most exciting, is the possibility that retrograde cerebral perfusion is actually providing nutrient flow supporting cerebral metabolism.

The failure of venous valves in the neck to prevent modest retrograde flow is fascinating but perhaps not astounding because humans and their predecessors have walked and lived upright (except during sleep) for two million years or more. Thus the venous valves above the heart have little functional importance and probably are vestigial. Once the blood column passes the neck, no further impediment to flow should be encountered because the venous sinuses of the brain are devoid of valves. It is also true that those parts of the body in which retrograde perfusion might be most problematical (the gastrointestinal tract, where two venous systems are present in series, and the extremities, where venous valves are really quite competent) have greater tolerance for ischemia.

Yasuura and associates are to be complimented on their innovative approach, but the safety and the physiology of the technique that they have used will certainly require further laboratory study and clinical confirmation.

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Mechanical Circulatory Assist Using Heparin-Coated Tube and Roller Pump System

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We have invented a mechanical circulatory assist system that uses a heparin-coated tube and a roller pump. Experimental left heart bypass was performed on 13 mongrel dogs for 24 hours without systemic heparinization. There were no significant changes in coagulation variables during the experiment, and pathological examination of internal organs after bypass revealed no evidence of thromboembolism. We applied this assist system to 13 patients who could not be weaned from cardiopulmonary bypass after an open heart operation. Left heart bypass was performed on 7 patients, right heart bypass on 1 patient, combined left and right heart bypass on 2, and venoarterial bypass without oxygenation on 3. Duration of support ranged from 5 hours to 21 days, and the pump flow rate ranged from 0.8 to 3.2 L/min. Eight patients were successfully weaned from this support, and 6 were discharged from the hospital. Examination of the tubes in the assist system revealed excellent antithrombogenicity for at least 3 days without systemic heparinization. There was no evidence of thromboembolism in brain, kidneys, lungs, or other organs. Because of its simplicity and antithrombogenicity, this mechanical assist system is beneficial for patients who cannot be weaned from cardiopulmonary bypass after open heart operations.

(Ann Thorac Surg 1992;53:659–65)

Patients with profound heart failure after a cardiac operation who do not respond to the maximal dose of inotropic agents or to intraaortic balloon counterpulsation require mechanical circulatory support. Although many types of pulsatile ventricular assist devices are available in many countries [1–3], the devices are costly and require complex driving consoles. Consequently, these mechanical assist devices are not readily available in the majority of institutions. Clearly, a simpler method such as a roller pump–driven system is preferable. However, circulatory assist devices using conventional polyvinyl chloride or Tygon tubing necessitate systemic heparinization, which can cause a severe bleeding tendency or systemic thromboembolism if the anticoagulation is inadequate. A simple and powerful method of circulatory assist that can be easily used without systemic heparinization is desirable.

With this in mind, we invented an integrated circuit system for mechanical circulatory assist (from inflow cannula to outflow cannula) that incorporates a heparinized hydrophilic polymer-coated tube (Anthron; Toray Industries Inc, Tokyo, Japan). This antithrombogenic tube has been widely used as an indwelling central venous catheter [4], a tube for temporary portal–systemic venous bypass [5], and as a shunt tube in aortic procedures [6].

Basic Experiments

Material and Methods

PREPARATION OF THE HEPARINIZED TUBE. We constructed a tubing circuit designed for roller pump–driven left heart assist. The circuit was 360 cm in length and had an 8-mm inner diameter in the pumping portion. The system comprised an inflow portion, tubing, a pumping portion, and an outflow portion, all with a seamless construction. The tube material was plasticized polyvinyl chloride coated with a heparinized hydrophilic polymer (Anthron) [7] over the entire inner surface and on the outer surface of the ends to be inserted into the vascular system.

IN VITRO TESTING. The circuit was driven by a roller pump without being filled with fluid for 3 days to test its mechanical durability. Then samples of tubing were examined by scanning electron microscopy.

ANIMAL EXPERIMENTS. We designed experiments to evaluate the antithrombogenicity of the tubing. Left heart bypass was performed for 24 hours on 13 mongrel dogs weighing 10.7 ± 1.25 kg. General anesthesia was induced with intravenous administration of sodium pentobarbital (25 mg/kg), and the left chest was entered through a left thoracotomy. Before every perfusion, the circuit was filled with saline solution, and the compression of the rollers against the tube in the raceway was adjusted to just occlude the tube. The inflow cannula was inserted into the left atrium, and the outflow cannula was inserted retrograde into the left carotid artery. Each revolution of the roller pump gives 10 mL of antegrade flow (Fig 1).

Left heart bypass with a flow rate of 300 mL/min (30 rpm), which corresponded to approximately 30% of car-

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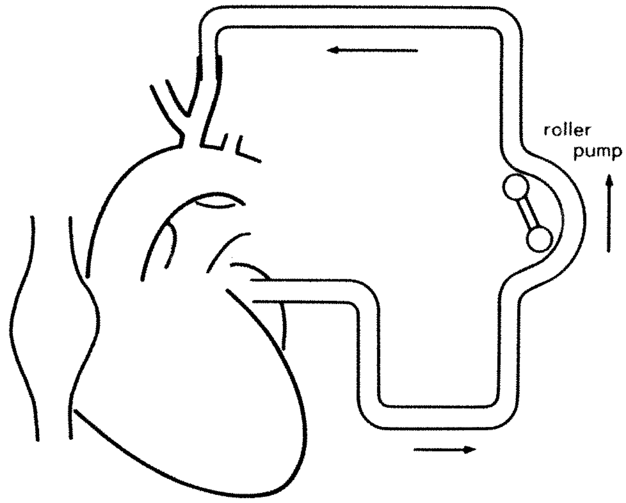

Fig 1. Left heart bypass in dogs. The venous cannula is placed in the left atrium and the arterial cannula, in the left carotid artery. The entire circuit, including the cannulas was treated with heparinized hydrophilic polymer and was driven by a roller pump.

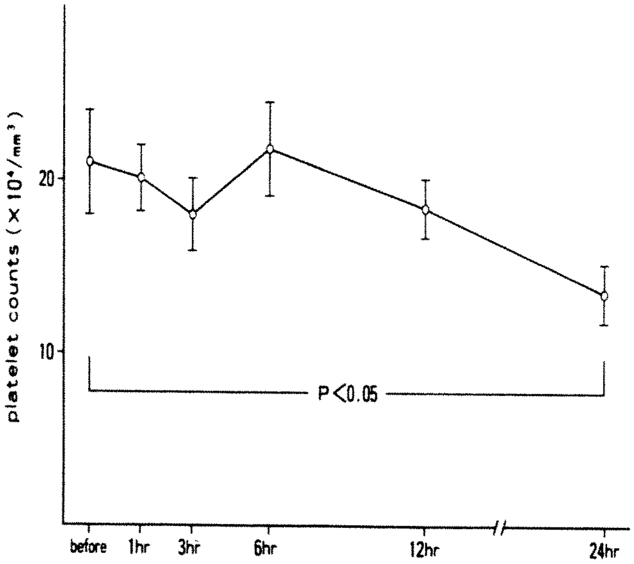

Fig 2. Platelet count during left heart bypass in dogs. Data are shown as the mean ± the standard error of the mean.

diac output, was instituted for up to 24 hours. No anticoagulant was administered. The electrocardiogram and right femoral arterial pressure were monitored continuously. Blood samples were taken before bypass and at 1, 3, 6, 12, and 24 hours after the initiation of left heart bypass. Activated coagulation time, platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, fibrin or fibrinogen degradation products, and plasma-free hemoglobin were measured in each sample. Serum and urine samples were collected at the same time as the blood samples to check for the presence of hemolysis.

Seven days after the bypass experiment, the dogs were sacrificed. They were examined both macroscopically and microscopically for the presence of thromboembolism in various organs including liver, spleen, heart, brain, kidneys, and intestines.

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Data are expressed as the mean ± the standard error of the mean. Statistical analysis was done with one-way analysis of variance among the sampling time points. A p value of less than 0.05 was considered significant.

Results

IN VITRO TESTING. The pumping portion of the tube had a longitudinal crease after 72 hours of being driven by a roller pump without being filled with fluid. No other portion of the circuit had findings of a crack or dissection, and the surface remained smooth.

ANIMAL EXPERIMENTS. Left heart bypass was maintained for 24 hours without complication in all 13 dogs. There were no significant changes in blood pressure and heart rate during left heart bypass with a flow rate corresponding to 30% of cardiac output. No thrombus formation was observed in the circuits after 24 hours of bypass. The only significant change in the hematologic data was a decrease in the platelet count 24 hours after the start of bypass ($p < 0.05$) (Fig 2). Other data including activated coagulation time, prothrombin time, activated partial thromboplastin time, fibrinogen, and plasma-free hemoglobin showed no significant changes (Figs 3–7). Fibrinogen degradation product values remained lower than 10 μg/mL. Noticeable hemolysis was not seen in any of the serum or urine samples. The autopsy findings revealed no thromboembolism in any of the internal organs examined.

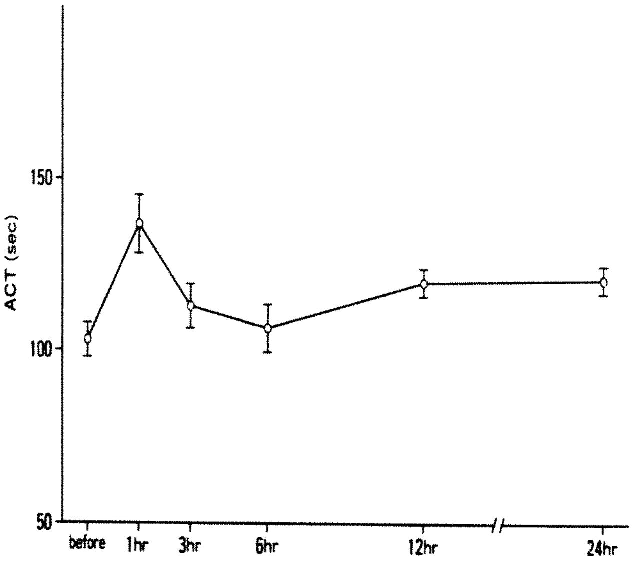

Fig 3. Activated coagulation time (ACT) during left heart bypass in dogs. Data are shown as the mean ± the standard error of the mean.

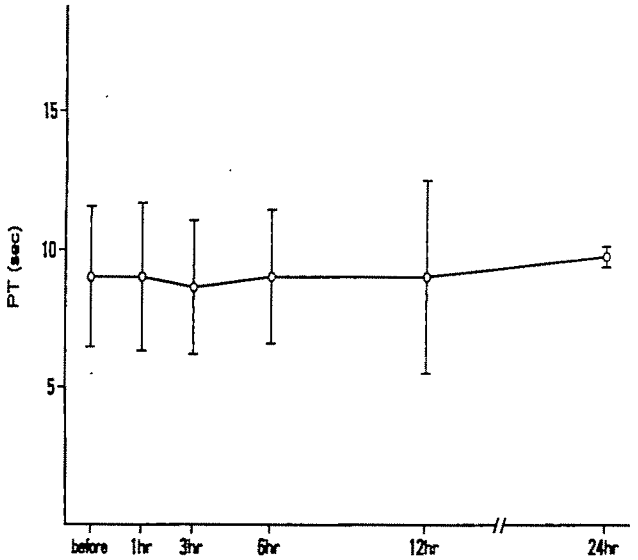

Fig 4. Prothrombin time (PT) during left heart bypass in dogs. Data are shown as the mean ± the standard error of the mean.

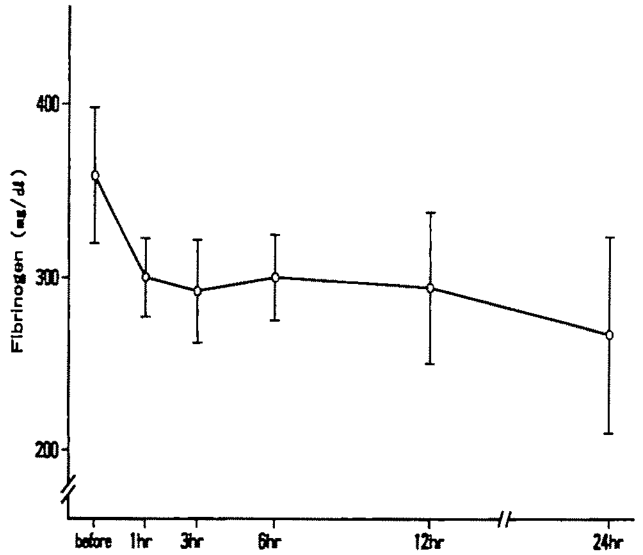

Fig 6. Fibrinogen during left heart bypass in dogs. Data are shown as the mean ± the standard error of the mean.

Clinical Application

Material and Methods

We devised several types of circuits for application to human circulatory assist. Different types of inflow and outflow cannulas and three sizes of pumping portion (inner diameter of ⅜ inch [9.375 mm], ½ inch [12.5 mm], and ⅝ inch [15.625 mm]) were prepared to adjust for the optimal flow rate. All the tubing circuits were made of polyvinyl chloride, and after the bypass system was set up, all blood-contacting surfaces were coated with a heparinized hydrophilic polymer (Anthron). The circuits were driven by a portable roller pump (Pemco, Cleveland, OH). After the circuit was primed with Hartmann's solution, the occlusiveness of the roller pump was adjusted to be just occlusive, as in the animal experiments.

Since April 1987, we have used this mechanical circulatory assist system in 13 patients (6 to 79 years of age) with profound heart failure after a cardiac operation (Table 1). Twelve patients could not be weaned from cardiopulmonary bypass, and in 1 patient, cardiogenic shock developed in the intensive care unit. The underlying diseases were ischemic heart disease in 5 patients, acquired valvular disease in 6, congenital anomaly in 1 patient, and arrhythmogenic right ventricular dysplasia in 1.

Left heart bypass was performed on 7 patients, right heart bypass on 1 patient, combined left and right heart bypass on 2, and venoarterial bypass without oxygenation

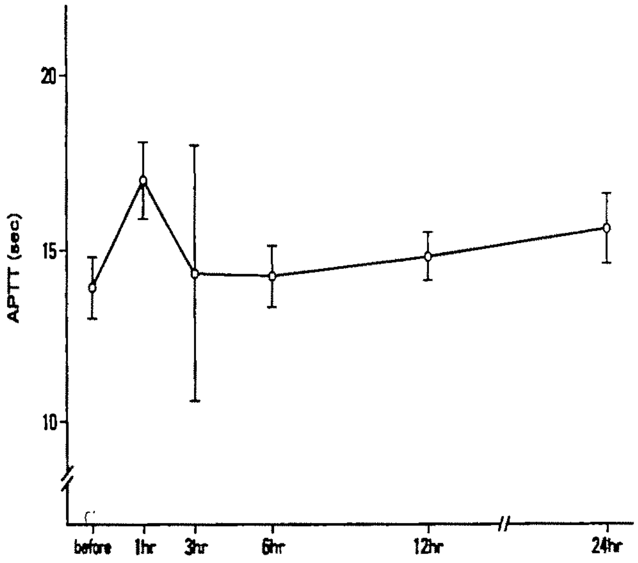

Fig 5. Activated partial thromboplastin time (APTT) during left heart bypass in dogs. Data are shown as the mean ± the standard error of the mean.

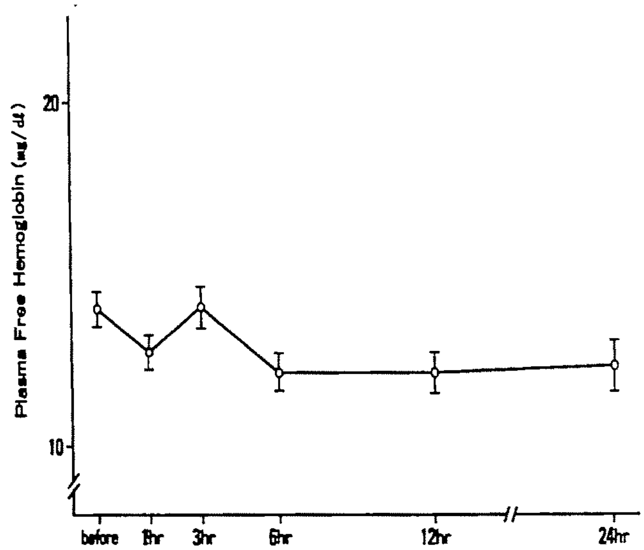

Fig 7. Plasma-free hemoglobin during left heart bypass in dogs. Data are shown as the mean ± the standard error of the mean.

Table 1. Summary of Patient Characteristics and Outcome

Patient No.	Age (y)	Sex	Diagnosis	Operation	Type of Support	Flow (L/min)	Duration	Outcome
Ischemic Heart Disease								
1	55	M	IHD	CABG	VAB	0.8	32 h	Alive
2	79	M	VSP	Repair	LHB	1.8	5 d	Died after 5 mo
3	67	F	VSP	Repair	LHB	1.5	25 h	Alive
4	52	M	IHD	CABG	LHB	2.0	64 h	Alive
5	47	M	IHD	CABG	LHB	3.2	4 d	Alive
Valvular Disease								
6	64	M	AR	AVR	VAB	1.0	13 h	Alive
7	42	M	MS + MR + AS + AR + TR	MVR + AVR + TAP	VAB	1.0	12 h	
					LHB	2.1	46 h	Not weaned
8	39	M	Root abscess after AVR	Root replacement	LHB	2.1	21 h	Not weaned
9	59	F	s/p AVR + MVR	Repeat AVR + repeat MVR	LHB+	3.0	2 d	Not weaned
					RHB	3.0	6 d	
10	62	M	MR + TR	MVR + TAP	LHB +	2.0	46 h	Alive
					RVAD	2.0	24 h	
11	56	M	MS + MR + AS + AR + TR	MVR + AVR + TAP	LHB	3.0	10 d	Died after 3 mo
Congenital Anomaly								
12	6	M	AV canal + TOF	Correction	VAB	1.2	5 h	Not weaned
Arrhythmia								
13	47	M	VT (ARVD)	Cryoablation	RHB	3.2	21 d	Not weaned

AR = aortic regurgitation; ARVD = arrhythmogenic right ventricular dysplasia; AS = aortic stenosis; AV canal = atrioventricular canal; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; IHD = ischemic heart disease; LHB = left heart bypass; MR = mitral regurgitation; MS = mitral stenosis; MVR = mitral valve replacement; RHB = right heart bypass; RVAD = right ventricular assist device; s/p = status post; TAP = tricuspid annuloplasty; TOF = tetralogy of Fallot; TR = tricuspid regurgitation; VAB = venoarterial bypass; VSP = ventricular septal perforation; VT = ventricular tachycardia.

on 3. For left heart bypass, we inserted an inflow cannula through double pursestring sutures into the left atrium and inserted an outflow cannula into the femoral artery through either a pursestring suture or a prosthetic tube sutured end-to-side to prevent lower limb ischemia (Fig 8). We rationalized that the potential for cerebral embolism would be substantially decreased if the femoral artery was used for inflow.

For right heart bypass, an inflow cannula was inserted into the right atrium, and an outflow cannula was inserted into the main pulmonary artery through pursestring sutures. We used venoarterial bypass for patients whose requirement for assisting flow was thought to be less than 1 L/min. An inflow cannula was placed into the right atrium or femoral vein through a pursestring suture and an outflow cannula, into the femoral artery in the same way as for left heart bypass. Intraaortic balloon counterpulsation was employed simultaneously in all patients.

After withdrawal of cardiopulmonary bypass, heparin sodium was reversed with protamine sulfate to keep hemorrhage to a minimum in the operative field. No anticoagulant was administered until the period of assist exceeded 3 days. At that point, we used heparin or the protease inhibitor nafamostat mesilate [8] for anticoagulation to maintain the activated coagulation time between 150 and 200 seconds.

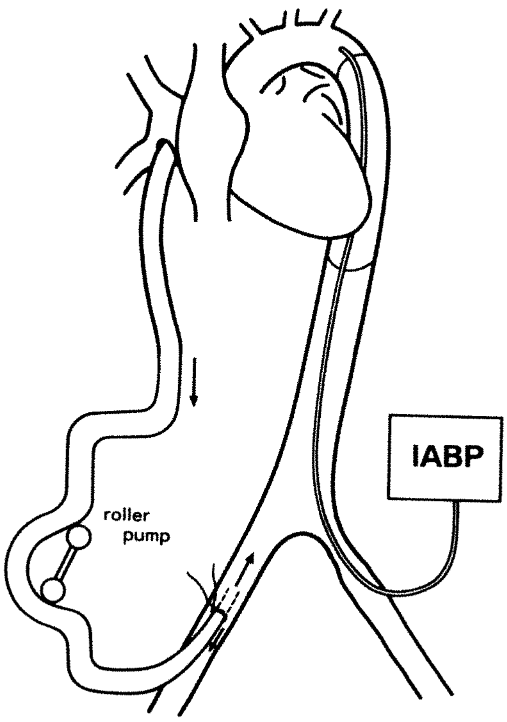

Fig 8. Left heart bypass in clinical practice. (IABP = intraaortic balloon pump.)

Platelet count, hemoglobin, activated partial thromboplastin time, fibrinogen, and fibrin or fibrinogen degradation products were measured every day during the assist period. Platelet counts of 10 patients whose assist time exceeded 24 hours were examined by comparing the value at initiation of assist with that 1 day later. Furthermore, platelet counts of 5 patients who required assist for more than 3 days were compared among the sampling time points. Urinalysis including measurement of urinary hemoglobin, bilirubin, and urobilinogen was performed every 8 hours to detect hemolysis.

Left atrial pressure, right atrial pressure, pulmonary arterial pressure, mixed venous (pulmonary artery) oxygen saturation, and cardiac output by thermodilution or the Fick method as well as the electrocardiogram and the radial artery pressure were monitored continuously. The optimal assisting flow rate was determined to keep the total flow (native heart output + assisting flow) greater than 2.8 L · min^{-1} · m^{-2}, the mixed venous oxygen saturation greater than 0.60, the left atrial pressure less than 20 mm Hg, and the right atrial pressure less than 15 mm Hg to prevent ischemic organ failure. In patients 11 and 13, whose assist period exceeded 6 days, we exchanged the tubing (once or four times) but left the inflow and outflow cannulas intact because of concern about the physical durability of the pump tubing. We attempted to wean patient 13 from support 13 days after the beginning of assist, and at that time exchanged the whole circuit, including the inflow and outflow cannulas.

On termination of perfusion, the tubing was immersed in phosphate buffer and fixed in glutaraldehyde, and the inner surface of the tubing was examined with a scanning electron microscope. The heparinized hydrophilic polymer, which coats this circuit, continuously releases heparin from the surface into the bloodstream. We therefore analyzed the heparin concentration in the tube after use for mechanical assist to assess the durability of the antithrombogenicity. Residual heparin in the tube was quantified by detecting the intensity of the Kα line of the sulfur atom of heparin using an x-ray microanalyzer [4].

Hematologic data are expressed as the mean ± the standard error of the mean. Differences in the platelet count before bypass and 1 day after bypass were assessed by paired Student's t test. One-way analysis of variance was used to compare platelet counts at each time point. A p value of less than 0.05 was considered significant.

Results

The duration of mechanical circulatory support ranged from 5 hours to 21 days (mean duration, 108 ± 128 hours [± standard deviation]), and the assisting flow rate ranged from 0.8 to 3.2 L/min (mean flow rate, 2.1 ± 0.8 L/min) (see Table 1). Eight patients (62%) were successfully weaned from support, and 6 (46%) were discharged from the hospital.

Platelet counts after 24 hours of assist in the 10 patients whose assist time exceeded 24 hours did not show any significant decrease (6.28 ± 0.99 versus $7.25 \pm 1.25 \times 10^{10}$/L [$6.28 \pm 0.99$ versus $7.25 \pm 1.25 \times 10^4/\mu$L]). The time of initiation of assist was the point of termination of extended use of cardiopulmonary bypass, and consequently the platelet counts were low for all patients. Platelet counts of the 5 patients requiring more than 3 days of assist revealed no significant changes among sampling time points (Fig 9).

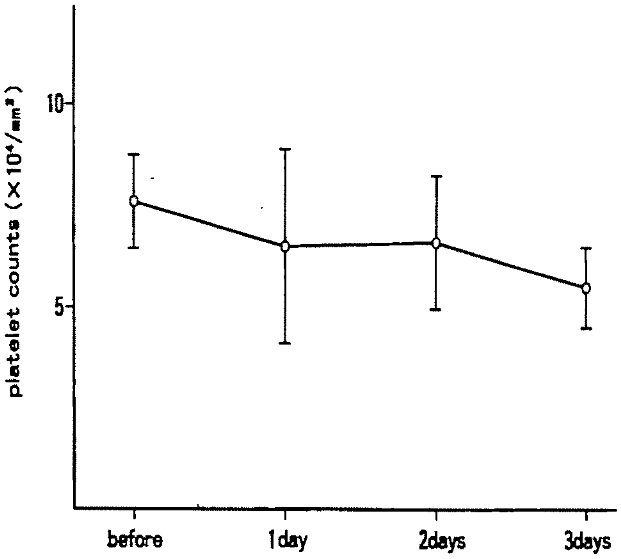

Fig 9. Platelet count of patients who required assist for more than 3 days at four time points: initiation of assist (before) *and on days 1, 2, and 3 after the beginning of assist. Data are shown as the mean ± the standard error of the mean.*

The values for activated partial thromboplastin time in all patients in whom no anticoagulant was used (period of assist did not exceed 3 days) were not prolonged compared with controls. The fibrinogen degradation product values were less than 10 μg/mL at all sampling points except for patient 9 (value of 20 to 40 μg/mL), who had severe hepatic failure. None of the patients showed any signs of thromboembolism.

All tubing used in this clinical trial was free from mechanical complications, including rupture, shearing, or fissuring. Thrombus formation was observed in 2 patients. In 1 of them, the tube was used for low-flow assist (0.8 L/min) for a period of 32 hours, and in the other, the pump tubing was used for more than 100 hours. The other tubes revealed no thrombus formation on the inner surface as assessed by macroscopic examination and by scanning electron microscopic inspection. There were attachments of platelets and red blood cells onto pump tubing perfused for more than 100 hours (Fig 10), although they were not formed into clusters.

By x-ray microanalysis, there were still traces of heparin in the tube used for 107 hours (Fig 11). The tube used for 126 hours without anticoagulation showed no residual heparin content. The pump portion of the tube had a greater tendency to lose the heparin coating than other portions. The inflow and outflow cannulas from patient 13 still had residual heparin after 13 days of continuous use. In spite of prolonged use of the roller pump, obvious hemolysis was not seen in any patient as evidenced by the fact that there was no demonstrable progressive anemia and hemoglobinuria, although we did not measure plasma-free hemoglobin in these patients. Three patients (patients 7, 9, and 13) underwent postmortem examina-

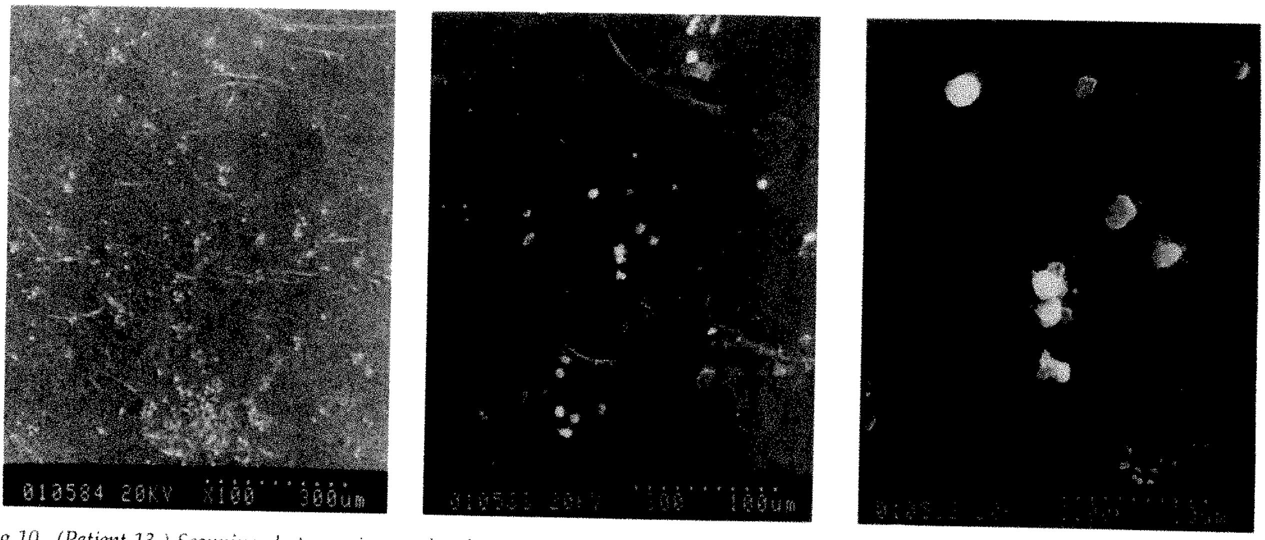

Fig 10. (Patient 13) Scanning electron micrographs of pump tubing explanted after 107 hours' use.

tion, and there was no finding of thromboembolism in the heart, liver, gastrointestinal tract, kidneys, or lungs. Severe liver congestion was seen in patient 9.

The 6 discharged patients have been followed up for 11 to 39 months (average follow-up, 28.5 months). There have been no late deaths. Three patients are in New York Heart Association functional class I, and 3 are in class II (Fig 12). Left ventricular function was examined by echocardiography during follow-up. Except for the patients with perioperative myocardial infarction, they showed relatively good left ventricular function (left ventricular ejection fraction, 0.55 to 0.66). None of the survivors have experienced any long-standing sequelae. Indeed, their quality of life is no worse than that of patients who did not require mechanical circulatory assist after a cardiac operation.

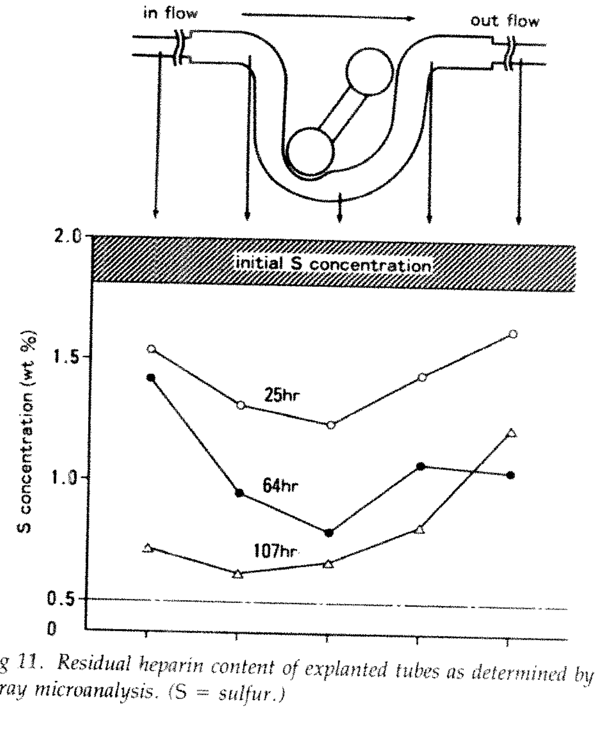

Fig 11. Residual heparin content of explanted tubes as determined by x-ray microanalysis. (S = sulfur.)

Comment

Cardiac surgeons now have available many types of mechanical circulatory assist devices for profound heart failure after open heart operations or for bridging to cardiac transplantation. These include a pneumatically driven pulsatile pump [1–3, 9], an electrically driven pusher-plate pump [10], and a centrifugal pump [11].

Pulsatile ventricular assist devices have been widely employed both for postcardiotomy cardiogenic shock and as a bridge to cardiac transplantation [12], and excellent results have been reported with their use. However, they are used only in select institutions, and they need complex driving consoles. In addition, their minimal recommended flow is high because fewer beats than the certified number (30 beats per minute) can lead to the possibility of thrombus formation [13]. Consequently, the devices necessitate the use of anticoagulation during the weaning period.

The centrifugal pump has been used for similar purposes. Although it has some beneficial aspects including economy and ease of operability, it necessitates the use of anticoagulation and should be changed at least every 48 hours because of its thrombogenicity and low durability [14].

We selected a roller pump as the assist device in view of its simplicity and availability. Mechanical circulatory assist with conventional polyvinyl chloride tubing necessitates systemic heparinization, which can cause severe bleeding. We applied a nonthrombogenic material, heparinized hydrophilic polymer (H-PSD, Anthron), to a circuit for mechanical circulatory assist driven by a roller pump. This polymer contains a large amount of heparin and continuously releases heparin from its surface into the bloodstream [15]. Therefore, as long as it theoretically elutes heparin, anticoagulation is not necessary. The polymer has also been applied to several kinds of cardio-

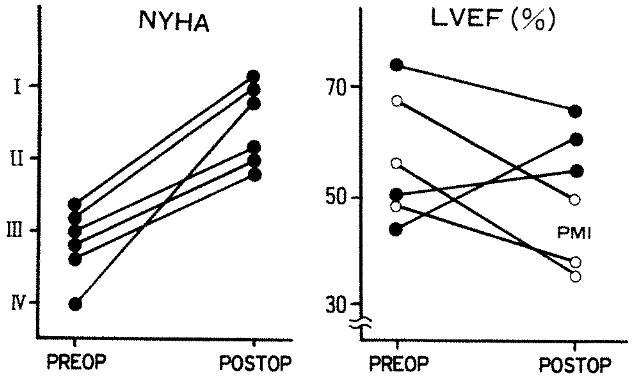

Fig 12. Cardiac function of long-term survivors. Open circles *indicate patients with perioperative myocardial infarction* (PMI). (LVEF = *left ventricular ejection fraction;* NYHA = *New York Heart Association.)*

vascular tubes and catheters, and it has demonstrated excellent antithrombogenicity for a long period. These catheters and tubes were all used with no external force. Our first concern was the rapid attenuation of the heparin in the segment of tubing because it would be continuously compressed by the roller pump. The findings on scanning electron microscopy of the tubing and the data on residual heparin from x-ray microanalysis suggest that the circuit retains its antithrombogenicity for at least 100 hours. The length of mechanical durability, ie, the period free from fissuring, rupture, or exudation, exceeds 150 hours, which was the longest time of use of one tube in this clinical series. If the assist period extended beyond 3 days, we administered heparin or a protease inhibitor, nafamostat mesilate, which inhibits not only coagulation but also fibrinolysis [8]. We also changed the circuits, exclusive of inflow and outflow cannulas, every 5 days to maintain antithrombogenicity and mechanical durability. This procedure was done easily and rapidly, and it had no effect on the hemodynamics of the assisted patient.

This assist system is very simple to use; only one physician and one well-trained nurse are necessary during the assist. It does not require any particular drive console or other special devices and therefore would be easy to implement in most institutions. In terms of expense, our assist system requires only a circuit, which costs much less than the other assist systems, and can be driven by a conventional roller pump. The maximum possible flow rate of this assist system exceeded 3 L/min when a large venous cannula (34F) was used. Although a roller pump cannot generate pulsatile flow, all patients in this series also had intraaortic balloon pumping.

Rose and co-workers [16] reported using a roller pump for mechanical circulatory assist, but they employed silicone tubing, which showed poor antithrombogenicity. Although they administered heparin to keep the activated clotting time between 150 and 250 seconds, the cases of some patients were complicated by severe neurological injury. In our study with heparin-coated tubing, there were no neurological deficits in any patient.

In conclusion, we are convinced that our simple mechanical circulatory assist system is very beneficial for the majority of patients in whom postcardiotomy cardiogenic shock develops.

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Beyond Cold Cardioplegia

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One hundred fifteen consecutive patients were operated on for myocardial revascularization or valvular disease or both with continuous antegrade and retrograde aerobic warm (37°C) blood cardioplegia. Mean cross-clamp time was 56.3 ± 21 minutes (± standard deviation). Mean reperfusion time was 18.4 ± 11.8 minutes (range, 5 to 81 minutes). Five patients (4.3%) died, and 15 (13%) needed inotropic support. Two (1.7%) required intraaortic balloon support. Two patients (1.7%) had evidence of perioperative myocardial infarction, and 98 (85%) returned spontaneously to normal sinus rhythm. Sixteen patients had a cross-clamp time greater than 80 minutes. All 16 of them had an uneventful postoperative course except for 1 patient who required inotropic drugs. This method of myocardial protection is now used for all open heart procedures in our institution.

(Ann Thorac Surg 1992;53:666–9)

Hypothermia has been the common denominator of almost all methods of myocardial protection since the beginning of cardiac surgery. Currently hypothermic cardioplegic arrest is the most widely used technique of myocardial protection, although the optimal composition of cardioplegic solution remains the subject of much debate.

Advances in cardiovascular surgical practice based on this technique have made heart surgery relatively routine, although poor results are still observed occasionally. It is the potential for such an occasional unpredictable failure that has led us to become interested in the new strategy of myocardial preservation developed by Lichtenstein and Salerno [1–4]. The rationale underlying their approach is based on the fact that a normothermic arrested heart requires about 90% less oxygen than a normothermic working heart [5–7]. The addition of hypothermia reduces oxygen demand by another 5% [8] but may have a detrimental effect on cellular integrity [9], enzymatic function [10], and energy generation [11]. Besides, hypothermic ischemic arrest may be followed by extension of injury resulting from reperfusion [12]. Therefore the concept developed by Lichtenstein and Salerno is that optimal myocardial protection can be achieved by continuous oxygenated, normothermic perfusion of an electromechanically arrested heart.

Material and Methods

Normothermic and aerobic cardioplegia was adopted at our institution in January 1991. Initially, to compare prospectively our results, every alternate patient had hypothermic blood cardioplegia. Nevertheless, we rapidly abandoned the cold technique in view of the obvious advantages of continuous normothermic cardioplegia: shorter cardiopulmonary bypass times, spontaneous return to normal sinus rhythm, and reduced use of inotropic drugs. Therefore, the present study only deals with the initial 115 patients who consecutively underwent continuous warm blood cardioplegia from February 1991 to April 1991.

The patient population consisted of 83 men and 32 women with a mean (± standard deviation) age of 61.9 ± 11.1 years (range, 28 to 85 years). Twenty-eight patients were older than 70 years of age (24.3%). Fifteen (13%) of the patients undergoing myocardial revascularization were operated on on an emergency basis, ie, within 24 hours after the decision to operate. Thirty-eight (33%) of the patients undergoing myocardial revascularization had had a previous myocardial infarction. Ejection fraction was less than 0.30 in 7 (6%) of the patients and ranged from 0.30 to 0.40 in 48 (41.7%). The surgical procedures are listed in Table 1.

Our operative technique closely followed that originally described by Lichtenstein and Salerno [1–4]. After median sternotomy and heparinization, cardiopulmonary bypass was established by means of an ascending aorta cannula and a single venoatrial cannula. Bicaval cannulation was used for mitral valve operations. Before initiation of cardiopulmonary bypass an aortic antegrade cardioplegia cannula (20012; DLP Inc, Grand Rapids, MI) was placed in the aortic root. A retrograde coronary sinus perfusion catheter (94415 RCSP cannula, 15F; DLP Inc) was inserted into the coronary sinus through the right atrial wall. Cardiopulmonary bypass was maintained at normothermia (37°C). With the heart empty and beating, a high-potassium [3] blood cardioplegia (blood diluted 4:1 with Fremes solution [3]) solution at 37°C was injected into the

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Table 1. Operative Procedure

Procedure	No. of Patients	
CABG		69
Single IMA ± RSVG	45	
Single IMA + extended endarterectomy + RSVG	3	
Multiple IMAs ± RSVG	17	
Multiple IMAs + GEA	1	
RSVG	3	
CABG + aortic valve replacement		5
CABG + mitral valve repair/replacement		2
CABG + multiple valve repair/replacement		2
Mitral valve repair		9
Mitral valve replacement		10
Aortic valve replacement		9
Bentall operation		1
Multiple valve repair/replacement		6
AV canal repair		1
ASD repair		1

ASD = atrial septal defect; AV = atrioventricular; CABG = coronary artery bypass grafting; GEA = gastroepiploic artery; IMA = internal mammary artery; RSVG = reversed saphenous vein graft.

aortic root after application of the aortic cross-clamp. Once cardiac arrest was obtained, the cardioplegia line was switched to the retrograde coronary sinus catheter and a low-potassium [3] warm blood cardioplegia was infused continuously at a flow rate of 100 to 150 mL/min. The infusion pressure at the cannula tip was maintained at less than 40 mm Hg.

During myocardial revascularization procedures, the root of the ascending aorta was vented while flow was maintained through the sinus cannula. We perfused the blood cardioplegic solution through vein grafts only on one occasion. The proximal anastomoses were performed during a single period of aortic cross-clamping [13].

Results

There were five operative deaths (4.35%): An 84-year-old woman died of aspiration pneumopathy on postoperative day 9 after aortic valve replacement. A 71-year-old woman died of multiorgan failure due to low cardiac output after aortic valve replacement. An 84-year-old woman with aortic and mitral valve disease (preoperative cardiac index, 1.4 $L \cdot min^{-1} \cdot m^{-2}$) died of low cardiac output after emergent double-valve replacement. A 64-year-old man died of septic complications after triple-vessel coronary artery bypass grafting. A 76-year-old man who underwent left ventricular aneurysmectomy and single coronary artery bypass grafting (preoperative ejection fraction, 0.36) died of low cardiac output on postoperative day 8.

Two patients required intraaortic balloon pump support for 4 and 18 hours, respectively. Fifteen patients (13%) required inotropic support for 4 to 48 hours. Two patients (1.7%) had electrocardiographic and cardiac isoenzyme evidence of perioperative myocardial infarction after coronary artery bypass grafting. Both of the infarctions were hemodynamically well tolerated. Ninety-eight patients (85%) resumed spontaneous sinus rhythm.

The mean reperfusion time (time elapsed between removal of aortic cross-clamp and weaning from cardiopulmonary bypass) was 18.4 ± 11.8 minutes (range, 5 to 81 minutes). Preoperative mean cardiac index was 2.7 ± 1 $L \cdot min^{-1} \cdot m^{-2}$. Postbypass mean cardiac index measured 20 minutes after weaning from cardiopulmonary bypass was 3.7 ± 1.4 $L \cdot min^{-1} \cdot m^{-2}$ ($p < 0.001$). The mean serum value for potassium measured immediately after the termination of the cardioplegic perfusion was 6.58 ± 1.08 mEq/L.

Comment

Aerobic myocardial protection with an arrested heart at 37°C is a new conceptual approach that has been proposed and used by Lichtenstein and Salerno [1–4]. Using their technique, we have obtained comparable results, which confirms the excellent quality of this method of myocardial protection.

In 3 patients we could not insert the retrograde coronary sinus catheter through the closed right atrium. The coronary sinus was cannulated under direct vision using the following procedure. The inferior vena cava was taped, the cavoatrial cannula pushed far into the cava, and the tape snugged over. The superior vena cava was cross-clamped and the right atrium opened. The coronary sinus was cannulated under direct vision and the right atrium closed. The superior vena cava was then unclamped and the cavoatrial cannula withdrawn into the right atrium. No clinical sequelae resulted from cross-clamping of the superior vena cava for short periods (5 to 8 minutes).

During the procedure it is important to ensure that retroperfusion is well maintained [14–16]. Cardiac veins engorged with oxygenated blood, good coronary sinus pressure, and return of dark blood through the aortic root vent indicate effective retroperfusion.

When the cannula with its occluding balloon is in the coronary sinus, the pressure curve at the cannula tip shows a depression every time the roller pump passes the point of minimal occlusion during each rotation (Fig 1). This depression disappears if the cannula becomes dislodged (Fig 2). Thus, in addition to allowing prevention of coronary sinus damage that could result from excessively high perfusion pressures, monitoring of perfusion pressure is helpful for checking the adequacy of positioning of the retroperfusion cannula.

The presence of blood in the lumen of coronary arteries does not really interfere with the construction of distal anastomoses, because the retrograde flow is only 100 to 150 mL/min. If necessary, small bulldog clamps can be placed on each side of the arteriotomy. Moreover, when necessary. retroperfusion has been reduced or even interrupted for periods less than 10 minutes. Lichtenstein and associates [1] report interruption of flow up to 15 minutes without any problem.

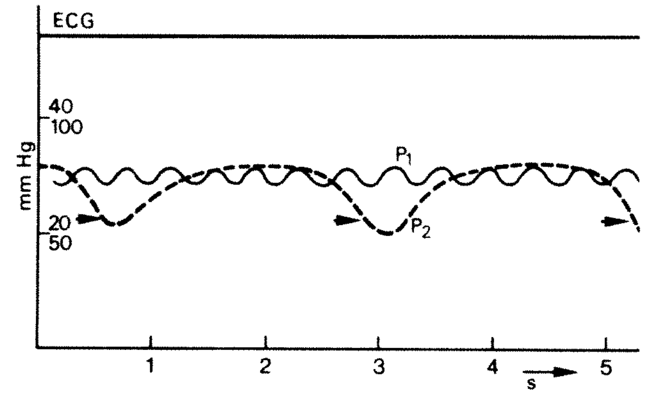

Fig 1. Characteristic curve at retroperfusion cannula tip during coronary sinus perfusion in an arrested heart (note the cyclical depression in pressure curve [arrow]*). (ECG = electrocardiogram;* P_1 *= arterial pressure curve [mean, 76 mm Hg];* P_2 *= coronary sinus pressure curve [mean, 26 mm Hg].)*

In conservative procedures on the mitral valve [17], myocardial tone is maintained during warm retrograde cardioplegic infusion, making assessment of the mitral lesions easier and more accurate throughout the procedure.

When hypothermia is used as a method of myocardial preservation in redo valve operations, it is necessary to mobilize the whole heart for effective topical cooling. We have been able to perform three redo valve operations with minimal mobilization, thus avoiding a host of complications and morbidity associated with extensive dissection.

In this series of various procedures, the mean cross-clamp time was 56.3 ± 21.0 minutes (range, 8 to 118 minutes). Sixteen patients had a cross-clamp time greater than 80 minutes. There were no deaths among them. Twelve of them returned spontaneously to normal sinus rhythm, and only 1 needed inotropic support for 36 hours. None of them required an intraaortic balloon pump, and there was no electrocardiographic or cardiac isoenzyme evidence of perioperative myocardial infarction. Long cross-clamp time was not associated with any serious cardiac morbidity.

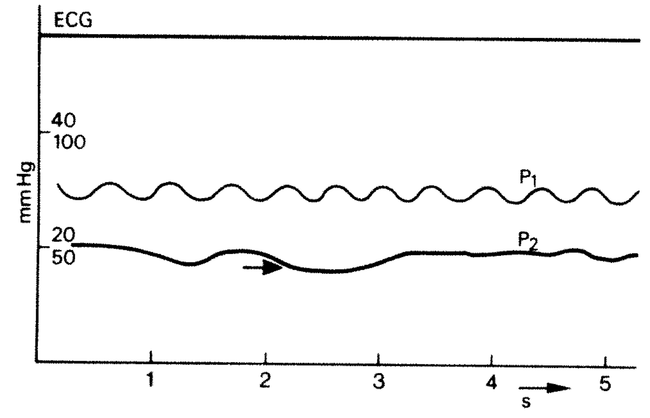

Fig 2. Curve at retroperfusion cannula tip if it gets dislodged from the coronary sinus (note the absence of cyclical depression in the pressure curve [arrow]*). (ECG = electrocardiogram;* P_1 *= arterial pressure curve [mean, 76 mm Hg];* P_2 *= pressure at the retroperfusion cannula tip [mean, 19 mm Hg].)*

Mean reperfusion time for the overall series was 18.4 ± 11.8 minutes (range, 5 to 81 minutes). There was no significant difference in reperfusion time between patients with cross-clamp times greater than 80 minutes (reperfusion time, 22.9 ± 12.1 minutes) and patients with cross-clamp times less than 80 minutes (reperfusion time, 17.7 ± 11.7 minutes).

In conclusion, this method of continuous aerobic normothermic cardioplegic arrest allows a smooth conduct of operations, permitting the safe and unhurried performance of complex procedures. Notwithstanding that this study is purely observational and does not include comparison with our previous conventional technique of cold cardioplegic arrest, it has been our impression that warm cardioplegia resulted in at least as good postoperative outcomes as with other currently used methods.

We are indebted to Dr Lichtenstein and Dr Salerno for their precious help at the time of our visit to their institution.

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Notice From the Southern Thoracic Surgical Association

The Thirty-ninth Annual Meeting of the Southern Thoracic Surgical Association will be held at the Saddlebrook Golf and Tennis Resort, Wesley Chapel (near Tampa), Florida, November 5–7, 1992. The Postgraduate Course will be held the morning of Thursday, November 5, 1992, and will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Members wishing to participate in the Scientific Program should submit an original abstract and one copy by May 15, 1992, to Walter H. Merrill, MD, Program Chairman, Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267. Abstracts must be submitted on the Southern Thoracic Surgical Association abstract form. These forms may be obtained from the Association's office or in this issue of *The Annals of Thoracic Surgery*. Manuscripts of accepted papers must be submitted to *The Annals of Thoracic Surgery* prior to the 1992 meeting or to the Secretary-Treasurer at the opening of the Scientific Session.

Applications for membership should be completed by July 1, 1992, and forwarded to John P. Clarke, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267.

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Coronary Artery Operation in Radiation-Associated Atherosclerosis: Long-Term Follow-up

George L. Hicks, Jr, MD

Cardiothoracic Surgery, University of Rochester Medical Center, Rochester, New York

Radiation-associated coronary atherosclerosis is a potential problem for patients who have had mediastinal irradiation for malignant tumors. This study identifies 14 patients with radiation-associated coronary atherosclerosis, defines unique population characteristics, and analyses postsurgical problems and long-term outcome. Fourteen patients with radiation-associated coronary atherosclerosis and class III and IV New York Heart Association symptoms were identified because of mediastinal or chest wall irradiation (30 Gy) associated with anterior epicardial discoloration or fibrosis, aortitis with adventitial thickening, and inflammatory process over a proximal coronary artery. Two distinct treatment groups were analyzed. Coronary artery operation resulted in one hospital death, with vein grafts being used predominantly. The internal mammary artery could only be used in 3 patients because of vessel friability and mediastinal fibrosis. Postoperative right ventricular dysfunction and pulmonary problems were frequent. Severe pericardial inflammatory complications (fibrosis with graft closure, and constrictive pericarditis) present in 2 early patients resulted in routine anterior pericardiectomy after coronary artery operation without further problems. Long-term follow-up (100%) (range, 11 to 74 months) revealed that 1 patient died late and of the remainder (12 patients), 11 were in New York Heart Association class I and 1 in class II, experiencing three myocardial events. Thus, patients with radiation-associated coronary atherosclerosis have a low operative mortality but have risk of early right ventricular and pulmonary dysfunction. The routine use of internal mammary artery may not be possible and anterior pericardiectomy is recommended. Long-term results are excellent and no evidence of accelerated disease has been noted.

(Ann Thorac Surg 1992;53:670–4)

Mediastinal irradiation is a commonly used treatment for Hodgkin's disease and for lung and breast carcinoma. In the early years, although it was demonstrated that lung injury could occur with radiation exposure, the heart and coronary vessels were believed to be radioresistant. However, studies from Stanford University involving patients who had received mediastinal irradiation for Hodgkin's disease revealed a number of patients with radiation-induced cardiac injury [1–3]. Subsequently, several authors have documented both experimental and clinical aspects of radiation injuries to the heart and coronary vessels [4–14]. Patients cured of their mediastinal tumor are therefore at increased risk for pericardial disease, myocardial fibrosis, or accelerated coronary atherosclerosis [15, 16]. This population requires close and long-term follow-up for their potential cardiac complication.

The successful treatment of this unique subset of patients with radiation-associated coronary atherosclerosis has been documented [17–19]. The purpose of this study was to identify a group of patients with radiation-associated coronary atherosclerosis who required coronary artery operation and analyze their unique postoperative problems, complications, and long-term outcome.

Material and Methods

The patients included in this prospective study are part of a cohort of more than 2,000 patients operated on by one surgeon (G.L.H.) at the University of Rochester Medical Center between June 1981 and January 1989. From this large group requiring coronary artery operation, 14 patients were identified as a subset who had presumed radiation-induced coronary artery disease. The inclusion of patients into the study group necessitated specific findings at operation consisting of: (1) inflammatory arteritis over the area(s) of vessel obstruction, (2) proximal lesions within the field of irradiation, and (3) visual evidence of myocardial fibrosis or fibrotic changes of the aorta or innominate vein.

The preoperative symptoms ranging from cardiogenic shock to unstable angina were similar to operative indications for other patients undergoing coronary artery operation, with angina unresponsive to medical therapy being most common.

Standard operative techniques consisted of a median sternotomy, routine aortic and atrial cannulation, and nonpulsatile cardiopulmonary bypass with moderate systemic hypothermia (30°C). Cold blood cardioplegia (10° to 12°C) and topical cooling were used for myocardial protection. The internal mammary artery was used whenever possible, and saphenous vein harvested from the lower extremity was used for additional grafts.

Preoperative, operative, and follow-up patient data are summarized in Table 1. Because two distinct groups were present based on type of malignancy and radiation treatment, the general patient data (Table 1) were reorganized according to tumor type (Table 2). Group 1 (n = 8) patients received mantle irradiation for Hodgkin's disease

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Table 1. Individual Patient Data

Patient No.	Age (y)	Sex	Tumor	Radiation Type	Years Since Diagnosis	Coronary Disease	Operation	Short-Term Results	Long-Term Results
1	80	F	Breast	McWhirter	20	2-vessel	CABG × 3, pericardiectomy	Good	Class I (35 mo)
2	63	M	Laryngeal	Neck/ Mediastinal	5	3-vessel	CABG × 4 (LIMA)	Excellent	Class I (25 mo)
3	65	F	Breast	Chest wall axilla	25	3-vessel	CABG × 4 (LIMA)	Excellent	Class I (11 mo)
4	71	F	Breast	Chest wall	12	3-vessel	CABG × 3, pericardiectomy	Died (RV failure)	
5	45	M	Hodgkin's	Mediastinal	18	3-vessel	CABG × 4, pericardiectomy	Excellent	Class I (45 mo)
6	59	F	Breast	McWhirter	17	Prox LAD	CABG × 1, division of fibrosed innom vein pericardiectomy	Good	Class I (19 mo)
7	39	M	Hodgkin's	Mediastinal	16	Left main	CABG × 4, pericardiectomy	Excellent	Class I (52 mo)
8	69	F	Breast	Chest wall and radium implants	19	3-vessel	CABG × 3, pericardiectomy	Dyspnea	Class I (10 mo)
9	48	M	Hodgkin's	Mediastinal	26	3-vessel	CABG × 4 (LIMA)	Mild RV dysfunction	Class II (30 mo)
10	50	M	Hodgkin's	Mediastinal/ abdominal	8	3-vessel	CABG × 3	Constrictive pericarditis, pericardiectomy at 6 weeks	Class I (74 mo)
11	53	F	Breast	Chest wall	5	2-vessel	CABG × 3, pericardectomy	Died at 6 months (?Arrhythmia)	
12	32	M	Hodgkin's	Mediastinal	12	3-vessel, s/p RV Infarct	CABG × 4, pericardiectomy	Excellent	Class I (74 mo)
13	36	F	Hodgkin's	Mediastinal	16	1-Vessel, RV Infarct w/shock	CABG × 1, pericardiectomy	Improved RV function by MUGA, normal ETT	Class I (27 mo)
14	35	M	Hodgkin's	Mediastinal	7	Left main	CABG × 2	Graft closure at 5 mo, reoperation: CABG × 2, pericardiectomy	Class I (72 mo)

CABG = coronary artery bypass grafting; ETT = exercise tolerance test; innom = innominate; LIMA = left internal mammary artery; MUGA = multigated acquisition scan; prox LAD = proximal left anterior descending coronary artery; RV = right ventricular; s/p = status post.

and group 2 (n = 6) received chest wall, mediastinal, and axillary irradiation for breast cancer.

Results

The patients were analyzed according to operative, postoperative, and follow-up findings.

Operative Findings

All patients had well-preserved (ejection fraction >0.45) left ventricular function, but 50% had moderate to severe right ventricular fibrosis estimated by visual appearance, failure of right ventricle to collapse with cardiopulmonary bypass, and elevated right atrial pressures preoperatively. Specific tests for right ventricular function were not performed preoperatively. Four patients (2 from each group) had mediastinal fibrosis with innominate vein contracture in 2. Although internal mammary artery dissection was attempted in most patients (92%) [13, 14], a usable conduit was obtained in only 3 patients. One patient had evidence of pericardial thickening, whereas "normal" pericardium was found in all other patients.

Postoperative Results

There was one hospital death (group 2) in an elderly patient with severe right ventricular fibrosis, pulmonary fibrosis and a pacemaker-dependent rhythm (Table 3).

As noted in Table 2, both groups exhibited a substantial

Table 2. Group Data

Group	n	Age (y)	Years Since Diagnosis	No. of Grafts	RV Fibrosis	Pulmonary Complications
Hodgkin's (group 1)	8	41	15	3.2	4/8	1/8
Breast cancer (group 2)	6	66	18	2.9	3/6	4/6

RV = right ventricular.

incidence of right ventricular fibrosis. Group 2 had more pulmonary complications, as defined by the necessity for prolonged intubation (>24 hours) or need for supplemental oxygen (>72 hours).

Both groups showed a marked dependence on normal sinus rhythm to optimize hemodynamics, and all surviving patients were discharged in sinus rhythm.

No sternal infections or neurologic or renal complications occurred.

Follow-up Results

Follow-up data were obtained from all surviving patients, ranging from 11 to 74 months. One patient in group 2 died of an acute arrhythmia 6 months postoperatively (Table 3). At 4 years, recurrent angina developed in 1 patient, necessitating angioplasty of a dominant right coronary artery; all bypass grafts were functional and patent. Two patients were hospitalized for myocardial events, one transmural and the other nontransmural infarction with uneventful recoveries.

Serious pericardium-related cardiac problems requiring reoperation developed in 2 of the first 3 patients in the study. One patient had severe constrictive pericarditis within 4 months necessitating pericardiectomy with complete clinical recovery. Postpericardiotomy syndrome with graft closure developed in the second patient at 3½ months, necessitating reoperation. Extensive fibrosis involving pericardium, mediastinal structures, and bypass grafts was evident. Because of the severity of these pericardial problems early in the series, subsequent patients have undergone anterior pericardiectomy routinely after conclusion of their coronary operation. No further early or late postoperative pericardial complications have been recognized.

Functional status on follow-up (Fig 1) was assessed in each patient according to New York Heart Association guidelines. The majority of patients (11) were in class I cardiac status, whereas only 1 patient was in class II.

Table 3. Follow-Up Mortality

Group	Hospital Deaths	Late Deaths	Mean Follow-up (mo)
Group 1	0	0	56
Group 2	1	1	18

Comment

Irradiation of the mediastinum has been a common treatment modality for several types of malignant tumors. Although radiation therapy can cure some mediastinal tumors, such as Hodgkin's disease, long-term secondary effects on mediastinal structures have been documented. Depending on the dose of radiation and the field of exposure, reports have documented radiation injury to the lung, pericardium, myocardium, conduction systems, valves, coronary arteries, and esophagus [4–14]. Because radiation injury is insidious and may take years to manifest itself, patients after mediastinal irradiation must be followed up closely for potential problems of the lungs, heart, and pericardium [13, 15, 16].

Patients with radiation-associated coronary atherosclerosis have some characteristic findings that can influence standard operative techniques. Radiation fields for Hodgkin's disease and breast carcinoma commonly include the course of the internal mammary artery. In this study, although many internal mammary artery dissections were tried, friability and inflammation of the internal mammary artery rendered it unusable in all but 3 patients. In general, women having orthovoltage irradiation after mastectomy had evidence of increased mediastinal injury. Four patients had frozen mediastina with fibrosed innominate veins and marked substernal scarring. Only 1 patient had evidence of a thickened pericar-

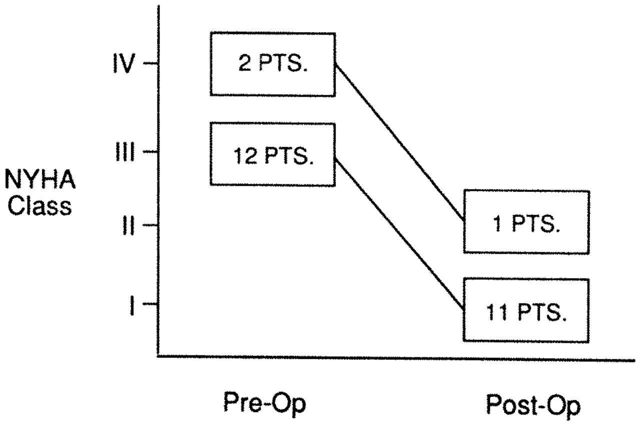

Fig 1. Radiation-associated coronary disease: functional status after coronary operation. (NYHA = *New York Heart Association.*)

dium, but because of 2 patients with early postoperative pericardial problems, anterior pericardiectomy was subsequently carried out in all remaining patients at the conclusion of the operation. Right ventricular fibrosis was present in half of the study group, and attention was given to optimizing right ventricular protection during cardiopulmonary bypass. Because of stiff, noncompliant right ventricles, normal sinus rhythm and its atrial "kick" played an important role in optimizing hemodynamics upon completion of cardiopulmonary bypass.

Postoperative complications (see Table 2) in this study group depended on the extent of radiation injury to the lungs and right ventricle and on the maintenance of normal sinus rhythm. Group 2 (breast cancer) patients had serious problems with pulmonary insufficiency characterized by prolonged intubation (>24 hours or oxygen dependence >72 hours), which was not present in group 1. This difference could be accounted for by the increased lung exposure to radiation in group 2 for treatment of their chest wall and lymph node areas. However, because of the difference in mean age between the two groups (41 versus 66 years), other age-related pulmonary factors could also be responsible. Hemodynamic stability was determined by right ventricular performance, as the majority of patients had good left ventricular function (ejection fraction >0.45). Right ventricular fibrosis was more common in group 1 patients but was present in both groups. Elevated right-sided pressures and normal sinus rhythm were necessary to optimize cardiac output in these noncompliant ventricles. The one death in this series was secondary to a combination of factors in a group 2 patient with severe left lung fibrosis, right ventricular dysfunction due to both fibrosis and infarction, and absence of sinus rhythm with a ventricular pacemaker.

Follow-up revealed the efficacy of revascularization in these patients; however, pericardial complications early in the experience mandated anterior pericardiectomy to minimize the risk of graft closure secondary to pericardial fibrosis or constrictive pericarditis. Transient right heart dysfunction and dyspnea were not uncommon, but by 1 month postoperatively, most patients were comparable with standard coronary artery operation patients, and at 6 months, all patients were functioning at the New York Heart Association class I level. Long-term survival has been excellent, with one death less than 6 months after operation secondary to an arrhythmia. Continued follow-up in these patients has failed to reveal deterioration in clinical right heart function, although this problem will be evaluated more precisely with future nuclear studies. Because these patients are at high long-term risk for graft atherosclerosis or progressive native disease and the internal mammary artery could not be used in the majority, early recurrence of symptoms might be anticipated. Thus far with 100% follow-up between 11 and 74 months, only 2 patients have recurrent angina, whereas the others remain asymptomatic.

Radiation-associated coronary artery disease must be considered in any patient undergoing radiation of the mediastinum (>30 Gy total dose). Techniques to decrease cardiac exposure have improved significantly over the years [20], including cardiac shielding, altering the depth of fields, and using computed tomography to deliver more precisely the calculated tumor dose. However, large numbers of patients have been treated with orthovoltage irradiation and imprecise techniques, and these patients should be evaluated over a long period for the insidious onset of coronary artery disease [16], right heart dysfunction, and pulmonary problems. Furthermore, because this population of patients is at increased risk for coronary atherosclerosis, risk factor modification should be an essential part of their health care plan.

This study documents the unique characteristics of patients with radiation-associated coronary artery disease. Hospital mortality after coronary artery operation is comparable with that of other coronary artery bypass patients. Long-term results with revascularization in radiation-associated coronary atherosclerosis have been excellent, but continued follow-up of this group will be necessary to assess any added risk of ventricular or coronary arterial changes secondary to radiation injury.

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Notice From the American Board of Thoracic Surgery

The part I (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas, TX, on February 7, 1993. The closing date for registration is August 1, 1992.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

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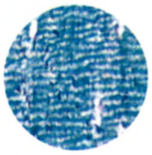

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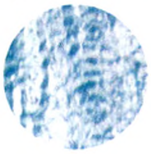

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Comparison of Late Pulmonary Function After Posterolateral and Muscle-Sparing Thoracotomy

Ronald B. Ponn, MD, Antoine Ferneini, MD, Richard S. D'Agostino, MD,
Allan L. Toole, MD, and Harold Stern, MD

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Muscle-sparing thoracotomy incisions have received considerable recent attention. There have, however, been few clinical and functional comparisons between the various approaches. The present study assessed early clinical results and late pulmonary function changes in 79 patients undergoing pulmonary operations by posterolateral, limited lateral, or transverse axillary thoracotomy. With the exception of wound seromas in the limited lateral group, there was no difference in rates of death or complications. Patients with muscle-sparing incisions showed significantly better late preservation of forced vital capacity and flow during the midportion of the forced vital capacity but not of other pulmonary volumes and flows. We conclude that limited incisions may result in slightly better late pulmonary function, but that the differences are small and of no apparent clinical advantage in the average patient.

(Ann Thorac Surg 1992;53:675–9)

The posterolateral thoracotomy has long been considered the standard incision for most thoracic surgical procedures. Wide operative exposure is provided by transection of the large muscles of the chest wall. In recent years the nearly universal use of stapling devices and selective lung ventilation has lessened the need for such extensive exposure. This has resulted in a growing interest in approaches requiring less muscle division, including median sternotomy, transverse and vertical axillary thoracotomy, lateral limited thoracotomy, and the serratus sling incision. Advantages claimed for the limited incisions include a better cosmetic appearance, less acute and chronic pain, improved chest wall and shoulder function, and a consequent smoother and faster recovery. Few clinical reports, however, have directly addressed these issues. The present study was undertaken to determine late, stable pulmonary function after two types of muscle-sparing incisions compared with posterolateral thoracotomy.

Material and Methods

Pulmonary Function Testing

Patients scheduled for routine segmentectomy, lobectomy, or pneumonectomy were included in the study. Those requiring concomitant chest wall, diaphragmatic, or other radical resections were excluded. In addition, patients having wedge excisions of small peripheral lesions were included only in the latter part of the study. Each surgeon employed his favored incision.

Flow rates and static lung volumes were determined by standard techniques before operation. Predicted postoperative values were calculated for each patient by the formula of Nakahara and associates [1]:

$$\text{predicted value} = \text{preop value} \times 1 - (b - n)/42 - n$$

where n is the number of obstructed subsegments and b is the total number of subsegments removed. The total number of pulmonary subsegments is 42, with the left upper and lower lobes having 10 each, the right upper lobe 6, the right middle lobe 4, and the right lower lobe 12. Subsegments were considered obstructed if there was more than 50% proximal blockage seen at bronchoscopy or if there was atelectasis, consolidation, or tumor replacement on computed tomography.

Testing was repeated postoperatively when the patient's clinical status indicated acceptable recovery from operation including minimal pain, return of energy and appetite, and a subjective sense of well-being. The observed postoperative volumes and air-flow rates were calculated as a percentage of the predicted levels.

The general clinical course of the groups was also assessed. Because most of the patients had peridural catheters for pain control during the initial 1 to 4 postoperative days, a valid comparison of incisional pain among the groups was not possible.

Incisions

Posterolateral thoracotomy is performed in the standard manner with division of the latissimus dorsi and anterior serratus muscles as well as the anterior portion of the trapezius, without resection or transection of ribs. For closure of both the standard and muscle-sparing incisions, the ribs are reapproximated with heavy absorbable

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Table 1. Characteristics by Incison Group of Patients Completing the Study ($n = 79$)[a]

Variable	PL	AX	LL	MS
No. of patients	17	15	47	62
Age (y)				
Mean ± SD	60 ± 9	65 ± 11	62 ± 12	62 ± 12
Range	47–71	41–84	28–88	28–88
Sex (M/F)	10/7	8/7	28/19	36/26
Subsegments/patient				
Mean ± SD	8.9 ± 5.5	6.5 ± 3.9	9.4 ± 5.3	8.7 ± 5.1
Range	0–22	1–12	0–22	0–22

[a] There were no significant differences between groups.

AX = axillary; LL = limited lateral; MS = combined muscle-sparing (AX + LL); PL = posterolateral; SD = standard deviation.

sutures passed above the upper rib and through holes punched in the lower rib, to avoid compression of the neurovascular bundle. The transected muscles are closed with continuous absorbable suture.

For the axillary approach an oblique incision below the hairline extends from the anterior border of the latissimus muscle to the submammary fold. The latissimus is retracted posteriorly. The serratus is divided in line with its fibers anteriorly only, to avoid damage to the long thoracic nerve. The intercostal muscles are opened well beyond the limits of the skin incision. A small retractor is used to spread the ribs. A second spreader is often placed at right angles to the first to retract the skin anteriorly and the latissimus posteriorly. The divided portion of the serratus is closed with running absorbable suture.

For the limited lateral thoracotomy the skin incision extends from the submammary fold at the anterior axillary line to a point just below the scapular tip. Subcutaneous flaps are developed. The anterior border of the latissimus is freed and retracted posteriorly, exposing the posterior edge of the serratus, which is then retracted anteriorly. On occasion some of the serratus insertions are freed from the ribs at or below the interspace entered, but the main body of the muscle is not divided. Two small retractors are placed at right angles to each other as with the axillary incision. No muscle closure is required because the serratus and latissimus are allowed to resume their normal positions. A Jackson-Pratt drain is positioned to evacuate the subcutaneous flap.

Results

A total of 90 patients were entered into the study. Two patients died in the perioperative period. One patient in the posterolateral thoracotomy (PL) group died of aspiration pneumonitis, and 1 in the muscle-sparing (MS) group of a massive pulmonary embolus. Four patients were considered too debilitated by adjuvant chemoradiotherapy to undergo valid late testing. Five additional patients either refused postoperative studies or were cared for out-of-state. Thus 79 sets of paired data were available for comparison. Standard posterolateral incisions were performed in 17 of these and muscle-sparing thoracotomies in 62, 15 of which were axillary and 47 limited lateral approaches.

Table 1 summarizes the clinical data. The two groups were similar in age, ratio of men to women, and the number of subsegments resected per patient. The early postoperative results in the 90 patients originally entered in the study are presented in Table 2, comparing the PL and combined MS groups. The length of postoperative hospitalization and the incidence of cardiac dysrhythmias requiring treatment, lobar atelectasis, parenchymal air leaks lasting longer than 5 days, and need for mechanical ventilator support beyond 2 days were similar in both groups. The only significant difference was the 11.8% incidence of wound seromas found exclusively as a complication of the limited lateral incision. Although occasionally sizeable, all seromas were painless and resolved within 6 weeks of operation without the need for aspiration or drainage in any case.

The results of postoperative pulmonary function tests compared with the predicted values are shown in Table 3. The studies were performed 6.4 ± 2.8 months after operation in the PL group and 5.1 ± 2.7 months after thoracotomy in the MS patients ($p = 0.08$, Student's t test). The limited thoracotomy groups generally demonstrated mean percent predicted postoperative flows and volumes that were higher than those measured in the PL patients. Statistically significant differences, however, were few. Significantly better preservation of forced vital capacity (FVC) was noted between the limited lateral and PL groups and between combined MS and PL groups. Significance was approached for FVC between the axillary and PL groups and for flow during the midportion of the FVC between the limited lateral and PL and combined MS and PL incisions. All other differences failed to reach or approach statistical significance.

The data were also assessed to determine the propor-

Table 2. Early Clinical Results in Posterolateral and Muscle-Sparing Thoracotomy Groups for All Patients Entering the Study[a]

Variable	PL	MS
Death	1 (4.5%)	1 (1.5%)
Postoperative stay (d)		
Mean ± SD	8.4 ± 3.6	8.6 ± 4.3
Range	4–20	5–33
Dysrhythmia	3 (13.6%)	5 (7.4%)
Atelectasis	2 (9.1%)	3 (4.4%)
Air leak > 5 days	2 (9.1%)	5 (7.4%)
Ventilator > 2 days	0	1 (1.5%)
Miscellaneous	0	1 brachial embolus
Wound seroma	0	8 (11.8%)

[a] The only significant difference is the incidence of seromas, all of which occurred in the limited lateral group.

MS = muscle-sparing; PL = posterolateral; SD = standard deviation.

Table 3. Pulmonary Function Tests[a]

Variable	PL	AX	LL	MS
FVC (L)				
Pred	3.03 ± 0.90	2.70 ± 0.78	2.53 ± 0.90	2.57 ± 0.88
Obs	2.84 ± 0.79	2.82 ± 0.78	2.66 ± 0.93	2.70 ± 0.89
% pred	95.6 ± 20.4	105.4 ± 13.7	106.5 ± 14.8	106.2 ± 14.6
p Value		0.133	0.023	0.019
FEV_1 (L/s)				
Pred	2.10 ± 0.68	1.97 ± 0.77	1.77 ± 0.66	1.82 ± 0.69
Obs	2.02 ± 0.60	1.95 ± 0.65	1.84 ± 0.64	1.87 ± 0.64
% pred	98.6 ± 19.6	101.2 ± 14.9	105.3 ± 16.0	104.3 ± 15.8
p Value		0.678	0.177	0.216
FEF_{25-75} (L/s)				
Pred	1.62 ± 0.91	1.54 ± 0.88	1.39 ± 0.96	1.43 ± 0.94
Obs	1.47 ± 0.86	1.47 ± 0.88	1.42 ± 0.89	1.44 ± 0.89
% pred	92.1 ± 20.2	99.2 ± 26.6	111.7 ± 41.8	108.7 ± 38.9
p Value		0.408	0.080	0.107
ERV (L)				
Pred	0.98 ± 0.50	0.74 ± 0.39	0.81 ± 0.48	0.79 ± 0.46
Obs	0.99 ± 0.48	0.89 ± 0.55	0.92 ± 0.44	0.91 ± 0.47
% pred	111.5 ± 45.5	136.3 ± 72.1	140.9 ± 88.9	139.9 ± 85.5
p Value		0.320	0.263	0.258
IC (L)				
Pred	2.18 ± 0.59	2.0 ± 0.59	1.82 ± 0.68	1.86 ± 0.67
Obs	2.06 ± 0.56	1.95 ± 0.50	1.81 ± 0.73	1.84 ± 0.69
% pred	96.9 ± 22.5	99.8 ± 20.2	100.6 ± 24.6	100.4 ± 23.7
p Value		0.745	0.634	0.634
FRC (L)				
Pred	3.18 ± 0.68	2.82 ± 0.82	2.80 ± 0.96	2.81 ± 0.93
Obs	3.29 ± 0.66	3.09 ± 1.11	3.00 ± 0.98	3.03 ± 1.02
% pred	105.2 ± 19.4	109.8 ± 21.0	109.5 ± 22.8	109.6 ± 22.5
p Value		0.602	0.566	0.539
RV (L)				
Pred	2.19 ± 0.61	2.06 ± 0.71	1.96 ± 0.76	1.98 ± 0.75
Obs	2.16 ± 0.66	2.25 ± 1.02	2.06 ± 0.77	2.10 ± 0.83
% pred	99.2 ± 30.7	108.6 ± 26.1	111.9 ± 39.1	111.2 ± 36.7
p Value		0.458	0.315	0.302
TLC (L)				
Pred	5.35 ± 0.92	4.87 ± 1.05	4.65 ± 1.36	4.71 ± 1.31
Obs	5.42 ± 0.82	4.90 ± 1.25	4.84 ± 1.38	4.85 ± 1.35
% pred	102.6 ± 16.9	101.4 ± 19.5	105.3 ± 16.7	104.5 ± 17.4
p Value		0.882	0.635	0.735

[a] *p* values compare AX versus PL, LL versus PL, and MS versus PL (Student's *t* test.)

AX = axillary; ERV = expiratory reserve volume; FEF_{25-75} = flow during midportion of FVC; FEV_1 = 1-second forced expiratory volume; FRC = functional residual capacity; FVC = forced vital capacity; IC = inspiratory capacity; LL = limited lateral; MS = combined muscle-sparing (AX + LL); Obs = observed value; % pred = percent predicted; PL = posterolateral; Pred = predicted value; RV = residual volume; TLC = total lung capacity.

tion of patients in each category with late function superior to that predicted. Table 4 compares the numbers of patients in the PL and combined MS incision categories whose postoperative pulmonary function was equal to or greater than predicted with those whose values fell short of the expected levels. The proportion of patients with better preserved function was uniformly higher with the limited incisions, but again reached or approached statistical significance only for FVC and flow during the midportion of the FVC.

Table 4. Number of Patients With Postoperative Flows and Volumes Greater or Less Than Predicted[a]

Variable	Group	Equal or Above	Below	*p* Value
FVC	PL	6	11	0.034
	MS	42	20	
FEV_1	PL	7	10	0.620
	MS	38	24	
FEF_{25-75}	PL	4	12	0.037
	MS	33	27	
ERV	PL	6	7	0.360
	MS	37	13	
IC	PL	6	7	0.999
	MS	21	29	
FRC	PL	7	5	0.840
	MS	34	12	
RV	PL	4	8	0.500
	MS	28	18	
TLC	PL	5	7	0.900
	MS	21	15	

[a] *p* values calculated by χ^2 test.

Abbreviations are as in Table 3.

Comment

Small incisions have intrinsic appeal for both patients and surgeons. It is, of course, important that the incision does not limit exposure and does not unduly prolong or otherwise compromise the planned diagnostic or therapeutic surgical task. Several reports have documented the feasibility of employing MS incisions for a wide variety of thoracic operations, ranging from lung biopsy to pneumonectomy [2–12]. Exposure is adequate for standard lymph node dissection, decortication, and some cases involving combined pulmonary and chest wall or diaphragmatic resection. All authors report satisfactory clinical results. Although it is clear that most procedures can be performed through MS incisions, the question of whether they offer any meaningful advantage over the standard PL approach has not been answered with certainty.

Hazelrigg and associates [13] presented a prospective, blinded study of 50 patients randomized to either limited lateral or PL thoracotomy. They found no difference in operative time for opening and closing the incisions. With the exception of a 23% incidence of seromas in the MS group, there was no significant difference in postoperative complications. Shoulder girdle strength at 1 week was maintained better in the MS group, but this difference was no longer present at 1 month after operation. The range of shoulder motion was similar for both incisions at 1 week and 1 month. Patients who had MS incisions required less narcotics during the first 24 hours than PL patients, but not after the first day. They demonstrated less perceived pain during the entire first week. Despite the pain differential, early postresection changes in pulmonary function, as determined by FVC and forced expiratory volume in 1 second at 1 week and 1 month, were similar for both groups.

Lemmer and colleagues [14] assessed a group of 28 patients randomized to PL or MS incisions. Again, hospital stay and complication rate did not differ between the two incision groups, with no wound problems in either category. Pain scales, narcotic need, and pulmonary function were assessed during the initial 24 hours after operation. In contrast to the other study, they found no difference in pain perception or morphine requirements, but did demonstrate better early preservation of FVC and forced expiratory volume in 1 second in the MS patients, but not of flow during the midportion of the FVC, alveolar-arterial oxygen gradient, or arterial carbon dioxide tension.

Although our patients were not randomized to MS or PL incisions, we believe that the comparisons are valid. Each incision was performed by a surgeon who routinely employs, is comfortable with, and indeed is an advocate of that particular approach. All other facets of patient management were similar. When the variable being studied is a technique, this type of patient assignment may be superior to randomization with each surgeon alternating procedures. In addition, we believe that comparing each patient's actual postoperative function with the level predicted on the basis of the amount of normal tissue resected is more meaningful than comparing group means alone.

We confirm the feasibility of using MS incisions for most pulmonary operations. Length of hospital stay and complication rates were unaffected by the type of incision employed. Although we did not formally assess early or late postoperative pain, we detected no clinically striking difference among the groups. It is also worthy of parenthetical note that we have not had to convert an MS into a PL incision because of operative exposure problems, either in this series or in our overall experience.

Gorlin and associates [15] showed that pulmonary function stabilizes by 6 weeks after thoracotomy. Before that time there are decreases in FVC, inspiratory capacity, expiratory reserve volume, functional residual capacity, and total lung capacity. Changes in timed forced expiratory volume are variable, and residual volume generally remains unaltered after operation. To reflect late stable function, our postoperative studies were done at least 2 months after thoracotomy and at a time when the patients were free of serious pain or other sequelae of operation that might interfere with the results. The data do not show a strong advantage for the MS incisions, but do suggest that there may be slightly better preservation of pulmonary function in this group. Although the differences were statistically significant in only a few instances, the MS patients demonstrated postoperative values that were consistently higher when compared with predicted levels than did the PL patients. Even when significant, however, the differences were small and of no apparent clinical importance. In addition, the MS patients seemed subjectively to recover slightly faster than the PL patients as evidenced by a shorter interval between operation and postoperative study that approached statistical significance.

Physiologically it is not surprising that any functional differences between the groups are small. The extent of the intercostal incision and the technique of rib reapproximation are the same for MS and PL approaches. These factors would be expected to have the greatest effect on both chest wall mechanics and postoperative pain. The large chest wall muscles that are left intact in MS thoracotomy, on the other hand, are considered only minor accessory muscles of respiration because they are inactive during quiet ventilation in normal humans [16]. This likely explains the findings of the current study as well as the conflicting data regarding early postoperative pain and pulmonary function reported previously. Although the small differences noted have not resulted in detectably improved recovery or fewer complications for the general spectrum of pulmonary surgical patients, it is conceivable that clinical correlation might be more apparent in a large series of patients with marginal preoperative function. We reiterate that our study examined late pulmonary function only and cannot be extrapolated to the early postoperative period.

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DNA Content in Correlation With Postsurgical Stage in Non–Small Cell Lung Cancer

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The relationship between DNA content, TNM stage, tumor size, grade, histology, and disease-free survival was assessed in a retrospective study of patients with non–small cell lung cancer who had undergone resection and complete mediastinal lymph node dissection. Flow cytometric analysis was performed on paraffin-embedded tissue of 90 consecutive patients. The patients were analyzed both as a group and by individual stage. Median follow-up was 11 months (range, 1 to 35 months). Aneuploid tumors were not significantly different from diploid tumors with regard to pathologic TNM stage ($p = 0.34$), size ($p = 0.5$), grade ($p = 0.5$), or histology ($p = 0.34$). Disease-free survival of patients with aneuploid tumors was not significantly different than that of patients whose tumors had normal DNA content ($p = 0.69$). DNA content did not correlate with established prognostic factors in patients with non–small cell lung cancer who underwent resection and complete mediastinal lymph node dissection.

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The accepted prognostic indicators for non–small cell lung cancer (NSCLC) are embodied in the TNM staging system [1]. These include tumor size and location, the presence or absence of intrathoracic nodal metastases, and the presence or absence of distant disease [2, 3]. Numerous investigators have recently evaluated tumor cell DNA content as an additional independent variable [4–21].

Flow cytometric analysis (FCA) provides information regarding cellular DNA content as well as cellular kinetics. Using either fresh or archival tissue, a single cell suspension is prepared and a fluorescent dye (propidium iodide) chemically bound to the DNA, which is excited when the cells are passed in single file through light with an appropriate wavelength. The fluorescence emission is collected and displayed as a DNA histogram [22]. Flow cytometric analysis of fresh and subsequently paraffin-embedded tissue yield similar values for DNA content.

The genetic information embodied within tumor DNA determines, in part, resistance to chemotherapeutic agents, tumor invasiveness, rate of cellular proliferation, and metastatic potential. The extra chromosomes contained in aneuploid tumors may contain the genes responsible for the metastatic process and deregulation of growth inhibition. Although this teleological prediction of aneuploid-induced aggressive tumor behavior is appealing, published reports offer conflicting data concerning the correlation of tumor cell DNA content with tumor recurrence, patient survival, and TNM stage. The purpose of this retrospective study was to determine the relationship between DNA content, TNM stage, tumor size, tumor grade, histology, and disease-free survival in patients with NSCLC who have undergone complete resection and mediastinal lymph node dissection.

Material and Methods

The records of all patients who underwent resection of NSCLC between July 1987 and May 1990 were retrospectively reviewed, noting patient's age, sex, tumor histology, tumor grade, surgical stage, tumor size, type of resection, time from operation to tumor recurrence, and survival. Complete mediastinal lymph node dissection was performed in all patients [23]. Lymph node levels were labeled by the definitions of the American Thoracic Society [24]. After resection of right lung tumors, all level IV, VII, VIII, IX, and X lymph nodes were removed. Lymph nodes in levels V, VI, VII, VIII, IX, and X were removed during a left thoracotomy. Tumors were pathologically staged according to the American Joint Committee on Cancer staging [1] and graded histologically using the modified World Health Organization classification [25].

Hematoxylin and eosin slides were reviewed and paraffin blocks chosen to maximize tumor volume and minimize debris. Nuclear material was isolated using the method of Hedley [26]. Briefly, 50-μm sections were cut from paraffin blocks and deparaffinized in xylene and rehydrated in a series of graded alcohols. Enzymatic digestion was done with 0.5% pepsin at pH 1.5 and 37°C for 30 minutes. The specimen was vigorously vortexed at 10-minute intervals. After 30 minutes, each specimen was pipetted vigorously and filtered through a 50-μm nylon mesh. Samples were loaded in a discontinuous sucrose

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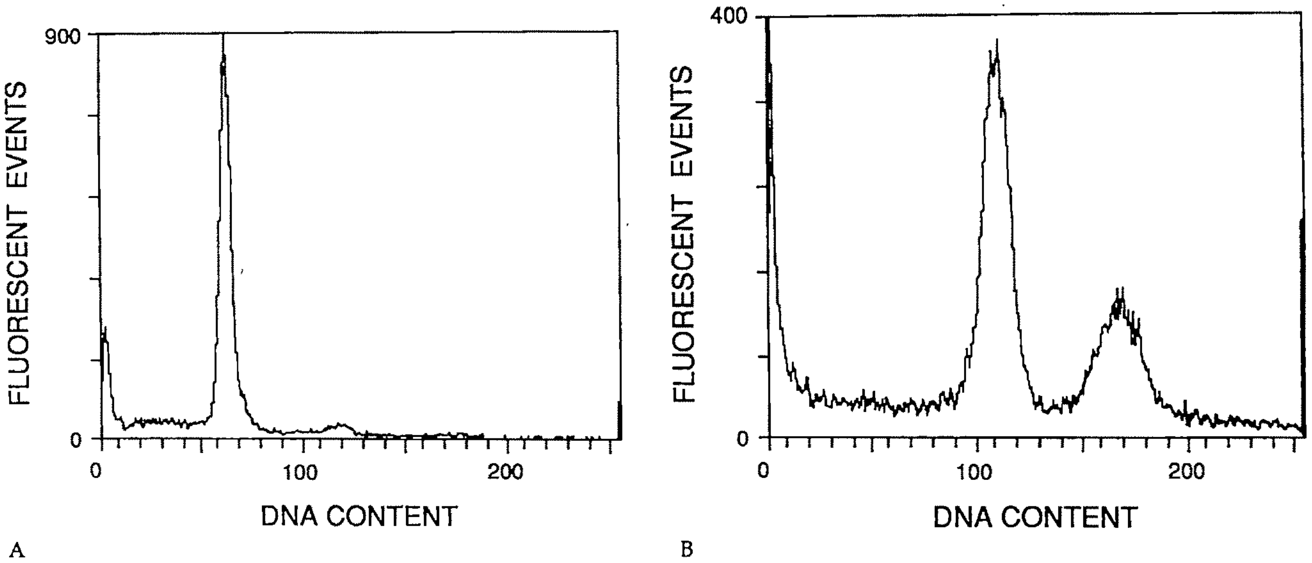

Fig 1. DNA histogram demonstrating (A) diploid peak with a single G1/G0 peak and (B) aneuploid peak with a shoulder to the right of the G1/G0 peak.

gradient consisting of 1.75 mol/L sucrose and 1.5 mol/L sucrose at 4°C before centrifugation at 2,500 *g* for 45 minutes. The pellets were washed in Dulbecco's modified medium containing 10% fetal bovine serum and resuspended in phosphate-buffered saline solution. Nuclei were resuspended in DNA fluorochrome buffer (0.04 TRIS, 5 mmol/L $MgCl_2$, 0.3% NP90, 0.05 mg/mL propidium iodide, and 1 mg/mL RNAse H, pH 7.0) and incubated for 35 minutes at 37°C. Before analysis, each sample was syringed through a 27-gauge needle and filtered through a 37-μm mesh. Samples were analyzed on a FacScan Flow Cytometer (Becton Dickinson, Surryvale, CA). Fifty thousand cells were read per sample.

The first G0/G1 peak of each histogram was assigned a value of 1.0 and interpreted as the diploid population. A second G0/G1 peak, a definitive shoulder to the right of the G0/G1 peak, or a G2M peak greater than 20% was required for a sample to be identified as aneuploid (Fig 1). A normal paraffin-embedded lymph node was used as a control. Histograms with a coefficient of variance greater than 8 were repeated with a new tissue sample. If the repeat histograms had a coefficient of variation greater than 8 or were uninterpretable, the samples were excluded. Because DNA histograms from paraffin-embedded material include a considerable amount of debris that complicates S-phase analysis, S-phase analysis was not reported.

Survival curves were drawn using the Kaplan-Meier method [27]. Statistical analysis for disease-free survival, defined as time from resection to tumor recurrence, was performed using the log-rank test. The remaining data were analyzed using the Fisher exact test and χ^2 tests.

Results

During the study interval, 90 patients with NSCLC underwent resection and complete mediastinal lymph node dissection. The 54 male and 36 female patients, whose ages ranged from 42 to 88 years (median, 64 years), had 47 pathologic stage I tumors, 6 stage II tumors, 31 stage IIIa tumors, and 6 stage IIIb tumors. There were 43 adenocarcinomas, 31 squamous cell carcinomas, 10 bronchoalveolar carcinomas, 5 large cell carcinomas, and 1 adenosquamous cell carcinoma. Eleven tumors were well differentiated, 32 moderately differentiated, 42 poorly differentiated, and 5 undifferentiated.

Due to excessive debris, nine tumors could not be evaluated. Aneuploid tumors represented 65.4% (53/81) of the study group. The coefficient of variation ranged between 1.1 and 8 (mean, 5.3). One patient died perioperatively and was excluded from survival analysis. Surgical procedures included 14 pneumonectomies, 64 lobectomies, 3 wedge resections, and 2 exploratory thoracotomies with biopsy. En bloc chest wall resection and lobectomy was performed in 7 patients. Median follow-up was 11 months (range, 1 to 35 months).

There was no significant difference between aneuploid and diploid tumors in regard to stage (p = 0.34), size (p = 0.5), tumor grade (p = 0.5), or histology (p = 0.34). Analysis of disease-free survival revealed no difference between aneuploid and diploid tumors when comparing all stages together (p = 0.69) (Fig 2). When analyzed by individual stage, there was no statistically significant difference between stage I aneuploid and diploid tumors (p = 0.2) or between stage IIIa and IIIb aneuploid and diploid tumors (p = 0.2) (Figs 3, 4).

Comment

Tumor DNA content and the distribution pattern of neoplastic cells among the phases of the cell cycle have been proposed as independent prognostic predictors for numerous malignancies, including NSCLC. The presence of abnormal DNA multiples (aneuploidy) or an increased

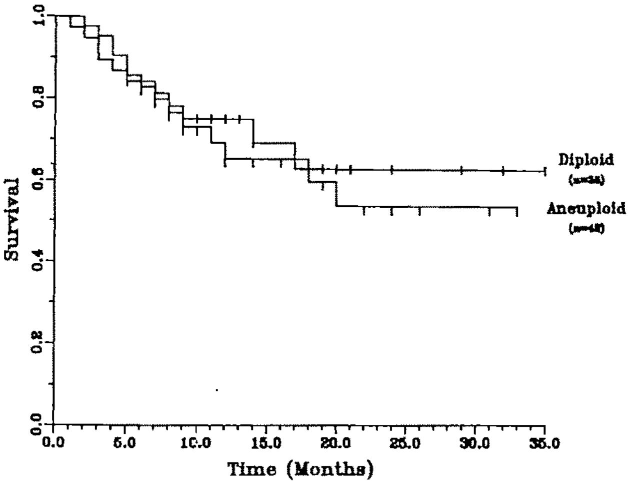

Fig 2. Kaplan-Meier survival curve for all stages of diploid and aneuploid non–small cell lung cancer.

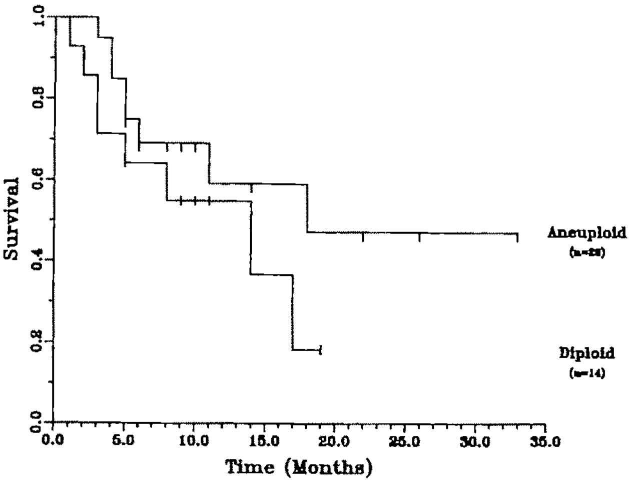

Fig 4. Kaplan-Meier survival curves for stage IIIa and IIIb diploid and aneuploid non–small cell lung cancer.

percentage of cells within the S (synthesis) or M (mitosis) phases of the cell cycle are thought to be associated with an aggressive clinical course [28]. However, the relationship between FCA and prognosis in patients with NSCLC remains unclear. The disparate published results may be due to sampling error within individual tumors, differing definitions of aneuploidy, or inaccurate surgical staging.

The prevalence of aneuploid tumors in patients with NSCLC varies between 55% and 96% [4–6, 8–11, 14, 16, 18, 21, 26]. Definitions of aneuploidy are similar, but not universal. All authors agree that the presence of a second G0/G1 peak is sufficient to establish tumor aneuploidy. However, in the absence of a second G0/G1 peak, the G2M peak becomes the crucial factor in histogram classification. The magnitude of the G2M peak considered necessary to establish aneuploidy varies, which may account for the discrepancy among different reports. The presence of aneuploid tumor in 65% of our evaluable patients is well within the reported range.

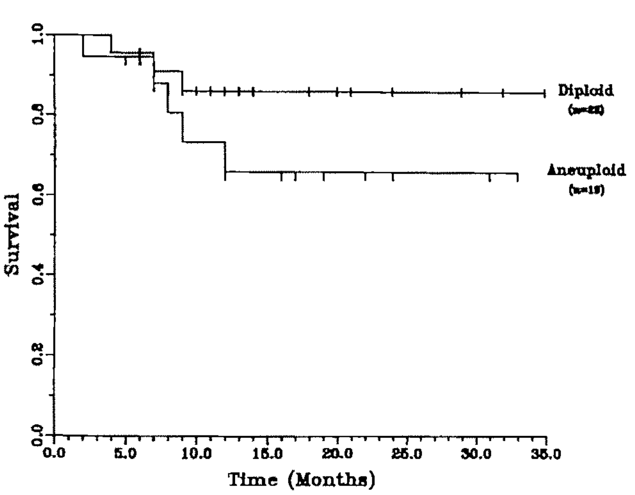

Fig 3. Kaplan-Meier survival curves for stage I diploid and aneuploid non–small cell lung cancer.

The uncertainties associated with FCA may be inherent in the technique. Photographically demonstrated karyotype that demonstrates both abnormal chromosome number and structure remains the standard against which FCA must be compared. Flow cytometric diploid tumors may have abnormal karyotypic structure [29]. Although Siegfried and associates [30] were able to show a good correlation between flow cytometry and the modal chromosome number of cultured primary NSCLC cells, there were a few patients who were diploid by FCA but aneuploid by cytogenetic karyotype. Therefore, regardless of the assumed definition of aneuploidy, there may be disagreement between FCA and the true karyotype. Karyotyping remains extremely labor intensive and, therefore, not yet suitable for analysis of large numbers of patients.

Standardization of surgical staging is necessary to accurately compare data between series. Complete mediastinal lymph node dissection, which was performed on all our patients, results in homogeneous pathologic stages. It is unclear whether other reported series are accurately surgically staged [14–21].

Our results are in agreement with those of both Cibas and co-workers [7] and Ten Velde and colleagues [16]. Cibas and co-workers reported no correlation between FCA and prognostic variables in 93 patients with stage I adenocarcinoma of the lung. Ten Velde and colleagues showed no correlation between NSCLC tumor aneuploidy and survival in 115 patients of various stages and histology. However, Volm and associates [8–12] reported that patients with aneuploid tumors had a significantly decreased survival as well as increased incidence of nodal and distant metastasis when compared with those patients with diploid tumors. In addition, those patients whose tumors had a greater percentage of cells in the S-phase had an increased incidence of metastasis as well as a decreased overall survival. Other authors have reported similar results [14, 17, 21].

In summary, our data do not support the use of

FCA-determined DNA content as an independent prognostic indicator in NSCLC. Furthermore, there appears no significant relationship between FCA-established aneuploidy and accepted staging. Larger prospective series, meticulous tumor sampling, standardization of the definition of aneuploidy, and accurate surgical staging are necessary to clarify the utility of FCA in NSCLC.

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Acute Pulmonary Edema After Blalock-Taussig Anastomosis

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Acute pulmonary edema developed in 2 patients after a Blalock-Taussig shunt procedure. Both patients had a univentricular heart complex with pulmonary stenosis. One patient underwent a modified Blalock-Taussig shunt using a polytetrafluoroethylene tube and the other underwent a classic Blalock-Taussig anastomosis. Acute pulmonary edema after the Blalock-Taussig shunt is rare, but once it has occurred, immediate treatment is obligatory.

(Ann Thorac Surg 1992;53:684–5)

Since introduction of the Blalock-Taussig procedure in 1945 [1], the systemic–pulmonary shunt has been a major strategy in the treatment of cyanotic children. The modified Blalock-Taussig shunt [2], interposing an expanded polytetrafluoroethylene graft between the subclavian and pulmonary arteries, has become increasingly popular as an alternative to the classic Blalock-Taussig shunt. One of the advantages of the Blalock-Taussig shunt is maintaining reasonably limited pulmonary blood flow by the diameter of the subclavian artery [2]. The following report deals with our experience in 2 rare cases of development of acute pulmonary edema due to excessive shunt flow through the Blalock-Taussig anastomosis.

Case Reports

Patient 1

A 16-month-old girl had been severely cyanotic since birth. When she was 9 months old, cardiac catheterization revealed a univentricular heart of the right ventricular type with pulmonary stenosis, atresia of the right atrioventricular valve, and right isomerism. Arterial oxygen saturation was 0.59. At operation, the diameters of the left subclavian artery and left pulmonary artery were 6 mm and 4 mm, respectively. A modified Blalock-Taussig shunt was constructed between the left subclavian artery and left pulmonary artery using a 5-mm-diameter tube made of polytetrafluoroethylene with 6-0 polypropylene running sutures. Shunt flow, measured using an electromagnetic flow meter, was 525 mL/min (1,329 mL $\cdot$ min^{-1} $\cdot$ m^{-2}).

Postoperatively, a transient rise in arterial oxygen saturation (0.82 with 100% oxygen) was followed by arterial oxygen desaturation (0.67 with 100% oxygen) and congestive heart failure. Chest roentgenogram (Fig 1) showed acute bilateral pulmonary edema, and a foamy red secretion was noted from the endotracheal tube. She received controlled ventilation with a positive end-expiratory pressure of 10 cm H_2O and required adrenaline and dopamine infusion for 4 days. Her general condition gradually improved and she was extubated on the fifth postoperative day, when her arterial oxygen saturation was 0.87 on room air.

Patient 2

Cyanosis in a 3-year-old-boy had first been noted when he was 7 months old. When he was 20 months old, a diagnosis was made of univentricular heart of the left ventricular type, pulmonary stenosis, transposition of the great arteries, common atrioventricular valve, total anomalous pulmonary venous return, and right isomerism. Arterial oxygen saturation was 0.45 on room air. At operation, the diameters of the left subclavian artery and left pulmonary artery were 7 mm and 6 mm, respectively. An end-to-side anastomosis was constructed between the left subclavian artery and the left pulmonary artery using 6-0 polyester sutures. Shunt flow, measured using an electromagnetic flow meter, was 1,260 mL/min (2,000 mL $\cdot$ min^{-1} $\cdot$ m^{-2}).

The oxygen saturation rose to 0.90 and he was extubated without difficulty on the following day. On the second postoperative day, however, he became dyspneic, and a chest roentgenogram (Fig 2) showed acute pulmonary edema primarily on the left side. At reoperation, the left lung was bright red and the shunt flow, again measured using the electromagnetic flow meter, had increased to 2,300 mL/min (3,650 mL $\cdot$ min^{-1} $\cdot$ m^{-2}). The Blalock-Taussig shunt (the left subclavian artery) was plicated longitudinally and the shunt flow decreased to 1,200 mL $\cdot$ min (1,905 mL $\cdot$ min^{-1} $\cdot$ m^{-2}). After reoperation, the patient's recovery was uneventful. Arterial oxygen saturation was 0.77 on room air.

Comment

The Blalock-Taussig shunt has several advantages over other systemic–pulmonary shunts. These include a lower incidence of excessive pulmonary blood flow, a lower

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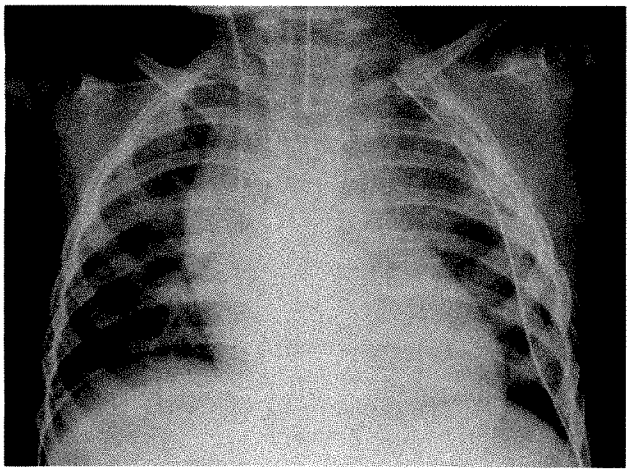

Fig 1. Chest roentgenogram of patient 1 after a modified Blalock-Taussig shunt.

incidence of pulmonary artery distortion, and simplicity of taking down the shunt during corrective operation [2]. Empirically, a rationale for the regulation of the shunt flow has been dependent on the concept that the diameter of the subclavian artery appears to be an ideal size for the shunt [2]. DeLeval and associates [2] concluded that a prosthesis of at least 5 mm should be inserted between the subclavian and pulmonary arteries without concern for overperfusion of the lungs, even in small infants. A microscopic study of the lungs of 46 patients who were operated on at the Johns Hopkins Hospital and who died within 1 week after a classic end-to-side Blalock-Taussig shunt disclosed that 11 patients had pulmonary arteriolar rupture and 23 patients had pulmonary capillary congestion and edema [3]. These findings were consistent with sudden excessive pulmonary blood flow.

There are some reports [4, 5] of the development of pulmonary vascular disease after the Blalock-Taussig shunt procedure. Taussig and associates [4] observed that among 601 patients who survived an end-to-side Blalock-Taussig shunt, 20 were diagnosed as having pulmonary hypertension. Hofschire and associates [5] reported that the incidence of pulmonary vascular disease increased with the time following the Blalock-Taussig shunt. Thus the concept of the flow regulation by the subclavian artery orifice diameter is not considered to be always safe. The diameter of the subclavian artery is generally larger than normal in cyanotic patients with right-to-left intracardiac shunts because of a larger systemic blood flow. The diameter of the subclavian artery also increases exponentially as patients grow. Practically, we think that the graft size has an important effect on the Blalock-Taussig shunt flow. Another factor causing acute pulmonary edema in our patients is attributed to the function of the systemic ventricle. Generally ventricular performance in the univentricular heart is suboptimal compared with that of other congenital heart anomalies that incorporate two ventricles [6].

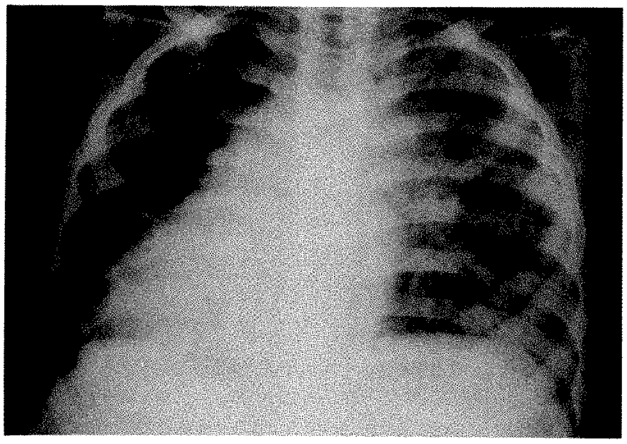

Fig 2. Chest roentgenogram of patient 2 after a classic Blalock-Taussig shunt.

Based on clinical experience, Chopra and associates [7] described the Blalock-Taussig shunt flow as ranging from 256 to 1,480 mL · min^{-1} · m^{-2}, with an average of 557 mL · min^{-1} · m^{-2}. These flows were equal to one-quarter to one-half of the child's normal cardiac output and provided the necessary pulmonary blood flow. One of us [8] reported that shunt flow should be maintained in the range of 1,600 to 2,400 mL · min^{-1} · m^{-2} or 30% to 40% of the systemic blood flow. Although the shunt flow in our patients was considered to be appropriate at the time of the operation, the shunt flow seemed likely to increase according to changes in pulmonary and systemic vascular resistance, and cardiac output, just as happened in patient 2.

Although the incidence of acute pulmonary edema and congestive heart failure after the Blalock-Taussig shunt is very low, it is a serious complication and requires early intervention, such as banding of the shunt, full medical support, and positive-pressure artificial ventilation. The bidirectional cavopulmonary shunt can be an alternative strategy of treatment for these patients with severely decreased pulmonary blood flow.

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Endobronchial Closure of a Postpneumonectomy Bronchopleural Fistula

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Successful permanent endobronchial closure of a serious postpneumonectomy bronchopleural fistula is reported in a patient with a delayed diagnosis of *Mycobacterium fortuitum-cheloni* infection. Increasing experience, improved plugging agents, and a review of the literature suggest that in selected patients, this procedure can avoid complex repeat operations and reverse life-threatening situations. Although atypical mycobacterial infections occur with infrequency, they are difficult to treat and may lead, as in this patient, to a misdiagnosis. Operations on granulomatous tissues are prone to heal poorly, thus inviting tissue breakdown and chronic fistulas.

(Ann Thorac Surg 1992;53:686–8)

A 64-year-old woman with a smoking history of 30 pack years who had stopped smoking 15 years before this illness was admitted 5 months before this admission with a diagnosis of pneumonia, which demonstrated incomplete resolution on appropriate antibiotic therapy. After 2 months of this therapy she underwent a bronchoscopy and needle biopsy with a negative result. With continuing incomplete resolution, a repeat bronchoscopy was performed 1 month before this admission, and biopsy was performed on a right upper lobe obstructing lesion. The histology was initially interpreted as adenocarcinoma (Fig 1). With this information—the long smoking history, a thin patient, and after a negative metastatic workup—the patient was transferred to a tertiary medical center for a right upper lobectomy.

At operation, due to the extensive encircling nature of the tumor and proximal location with involvement of the middle and lower lobes but an uninvolved mediastinum, the patient underwent an uncomplicated right pneumonectomy. The next day whole lung histology was reported as caseating granulomata tissue compatible with but not pathognomonic for tuberculosis (Fig 2). Two weeks after operation the patient had a low-grade fever and was finally discharged on a regimen of vancomycin and fluconozole with no firm bacteriological diagnosis.

One month after her pneumonectomy the patient was readmitted with increasing breathlessness and hypoxia, blood-tinged sputum, and fever. Her incision was erythematous and draining. Pulmonary embolus was ruled out with a negative pulmonary angiogram. A chest roentgenogram showed new loculated air pockets, and a diagnosis of postpneumonectomy bronchopleural fistula (BPF) was made. Closed chest drainage was instituted to evacuate the postpneumonectomy "empyema." A small air leak soon became clinically significant with respiratory embarrassment. Six weeks after her original pneumonectomy a Gelfoam (Upjohn, Kalamazoo, MI) plug was pressed into the fistulous tract, which was then overcoated with cryoprecititate and thrombin endoscopically. This terminated the air leak.

Four days later the incision was managed by secondary closure. Two weeks later and 1 day before definitive discharge, the microbiology cultures sent off several weeks previously grew an unidentified atypical mycobacterium, and broad-spectrum antituberculous therapy was instituted. However further laboratory investigations identified chemoresistant *Mycobacterium fortuitum-cheloni*, and all antituberculous therapy was discontinued. The patient continues to recover without evidence of disease progression, and a follow-up chest roentgenogram reveals no postpneumonectomy BPF.

Comment

Successful operation on a postpneumonectomy BPF can be a most challenging task. Most BPFs occur postoperatively, but many are recognized after use of ionizing radiation or after tuberculous, fungal, or bacterial diseases. Cancer and cancer chemotherapy, trauma, and ventilator barotrauma are recognized as triggers for BPF [1, 2]. The incidence of postpneumonectomy BPFs has steadily declined, presumably with better surgical management including bronchial staplers or absorbable versus nonabsorbable sutures, preservation of bronchial stump vascular supply, reduced manipulative trauma, and appropriate antimicrobial therapy. Also, strict port control of ionizing radiation has lowered the rate of postoperative bronchial stump necrosis.

Several different approaches attempting endobronchial BPF closure have been reported: glutaraldehyde-sterilized lead shot, fibrin glue, balloon occlusion, and Gelfoam and doxycycline/autologous blood patch [3–7]. In this instance, saline-soaked Gelfoam plugs were cut into tiny segments measuring ~0.5 × 1 mm and inserted down the

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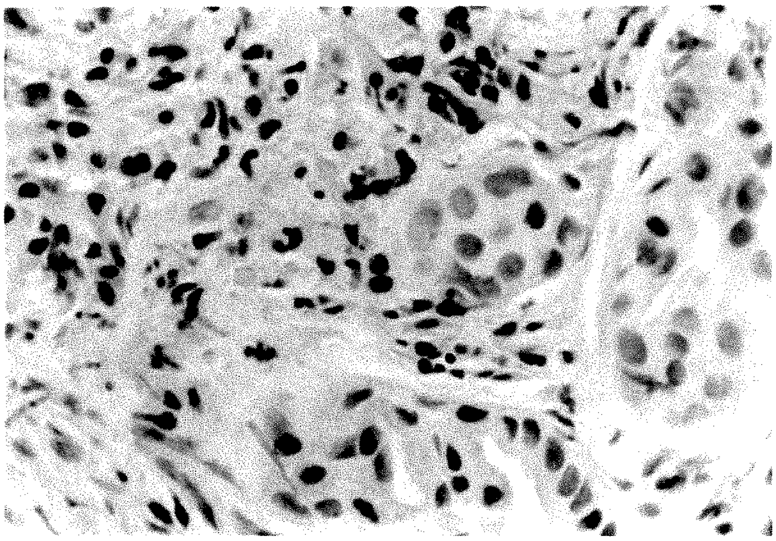

Fig 1. Submucosal glands with inflammatory atypia originally interpreted as adenocarcinoma. (Hematoxylin and eosin; ×40 before 39% reduction.)

biopsy channel of the fiberoptic bronchoscope in a microbiopsy forcep. The Gelform was then manipulated deeply into the postpneumonectomy BPF and released, effectively closing the leak. A small fibrin sealant cap was then made in situ by mixing limited amounts of cryoprecipitate and thrombin delivered through microcatheters inserted down the bronchoscope (Figs 3, 4). The glued Gelfoam plug was assisted into position by 48 hours of −20 mm Hg intrapleural suction. Ventilation was not used. The thoracostomy tube was removed after 2 weeks.

The postpneumonectomy BPF might have reopened if the antituberculous therapy had not commenced 2 weeks later, and we do not defend the effectiveness of the Gelfoam plugs without recognizing the role that antimicrobials play in other situations. However, in this instance, it was later determined that the infecting mycobacterium was chemoresistant, and antimocrobial therapy probably did not contribute to a successful outcome.

One of us (J.C.O.) has closed two other BPFs endoscopically using only fibrin glue: one after pneumonectomy, the other after lobectomy, both for extensive malignant disease with postoperative irradiation in one instance. One was permanently successful. The other recurred, requiring reentry. Had Gelfoam plugs been used this may have been avoided; however, new malignant cells were noted in the excised segment of the refashioned stump.

It is of practical importance to carefully monitor the volume of glue that is being injected. Should more than one minor bronchus be occluded, then a major ventilation catastrophe is likely before glue removal could be accomplished. This could result in asphyxiation.

More than 1 mL of fibrin glue is not recommended. Gelfoam plugs may be safer because they mechanically close the defect, which can then be coated internally with a small volume of fibrin glue. It may be useful in the future to presoak the Gelfoam in cryoprecipitate and antibiotic and then add thrombin through a catheter to form the internal fibrin patch. We did not find it necessary

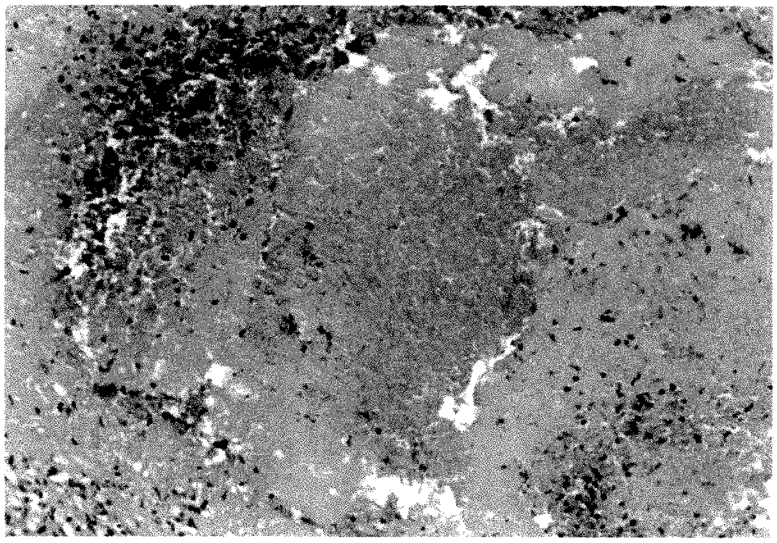

Fig 2. Pneumonectomy specimen of caseating granuloma. (Hematoxylin and eosin; ×10 before 39% reduction.)

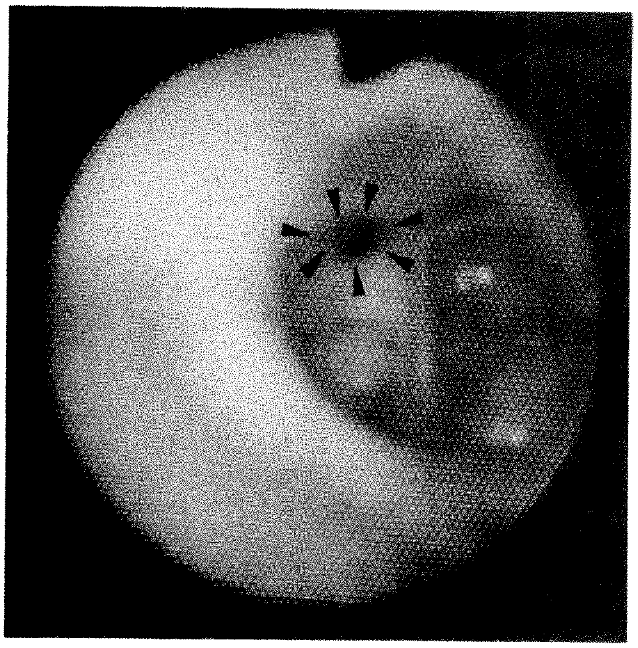

Fig 3. Endobronchial photograph of bronchopleural fistula.

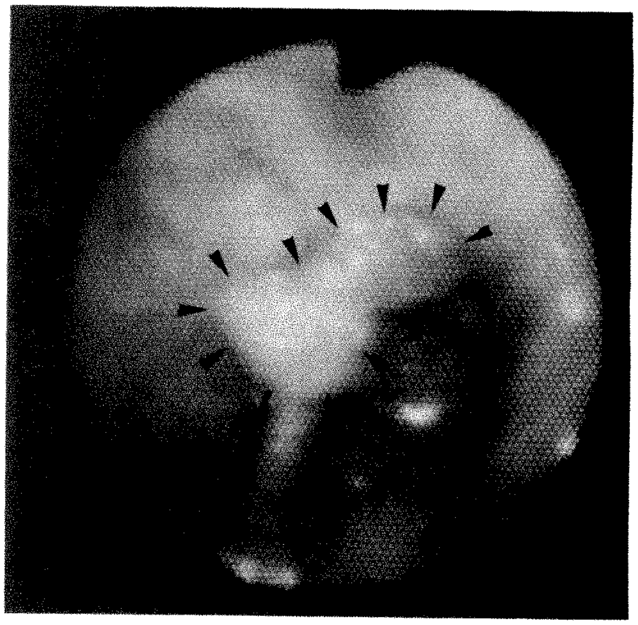

Fig 4. Endobronchial photograph of Gelfoam-plugged and fibrin-patched bronchopleural fistula.

to abrade the fistula with the aim of encouraging tissue ingrowth because of the risk of bronchial stump staple line breakdown. The plugs hold position satisfactorily with endobronchial fibrin glue and negative intrapleural suction.

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Pulmonary Resection and Contralateral Anomalous Venous Drainage: A Lethal Combination

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A 72-year-old acyanotic woman had development of acute right heart failure with systemic hypotension 2 hours after a curative right intrapericardial pneumonectomy for primary lung cancer. A postoperative pulmonary angiogram revealed a major left to right shunt through previously unsuspected partial anomalous venous drainage of the left upper lobe of the lung.

(Ann Thorac Surg 1992;53:689–91)

A 72-year-old female patient presented with massive hemoptysis of recent onset. Chest radiograph on admission showed atelectasis of the right middle and lower lobes of the lung (Fig 1). Urgent bronchoscopic assessment localized the source of bleeding to the right lung from a fungating adenocarcinoma of the bronchus intermedius. The pulmonary hemorrhage subsided with conservative management. The resectability of the tumor was then confirmed on the basis of adequate cardiopulmonary function, a computed tomographic scan of the chest showing a normal mediastinum, and a normal superior mediastinal lymph node biopsy.

Right thoracotomy under one-lung ventilation was performed, and intrapericardial pneumonectomy was carried out for stage I (T2 N0 M0) adenocarcinoma. A chest radiograph performed in the immediate postoperative period with the patient intubated confirmed a normal position of the mediastinum (Fig 2). Approximately 2 hours later, while she was still being ventilated, increasing hemodynamic instability developed with serious systemic hypotension with a systolic blood pressure of 60 to 80 mm Hg, a large alveolar-arterial gradient on an inspired oxygen fraction of 0.70 (arterial blood gas: pH, 7.27, carbon dioxide tension, 56 mm Hg; oxygen tension, 82 mm Hg; HCO_3, 26 mmol/L; oxygen saturation, 0.94), and acute right heart failure with a central venous pressure of 18 to 20 cm H_2O. Acute myocardial infarction was ruled out on the basis of a normal 12-lead electrocardiogram (and later by normal serum cardiac enzymes).

Emergency reexploration of the right thorax was performed for suspected cardiac herniation through the pericardial defect. At operation, although there was no evidence of cardiac herniation, it was obvious that the right heart was markedly dilated and the pericardium was tense with relative cardiac tamponade. Hemodynamic stability was partially restored after pericardiotomy and the infusion of inotropes. However, she continued to remain hypotensive; systolic blood pressure was less than 80 mm Hg with a worsening alveolar–arterial gradient, oxygen tension of 71 mm Hg on an inspired oxygen fraction of 0.7, and persistence of right heart failure (central venous pressure, 20 cm H_2O). A presumptive diagnosis of either massive pulmonary embolism or intracardiac shunt was entertained. An emergency pulmonary angiogram revealed a major left to right shunt through previously unsuspected partial anomalous venous drainage with the left superior pulmonary vein draining through a vertical vein into the left innominate vein (Fig 3).

The patient was returned to the operating room immediately, and surgical correction of the anomalous left to right shunt was performed under urgent cardiopulmonary bypass. The anomalous superior pulmonary vein was found on the anterior aspect of the left hilum; it measured 2.5 cm in maximal circumference and entered a seriously dilated innominate vein 4 cm from the innominate vein–caval junction. The anomalous vein was ligated at its entrance into the innominate vein and reimplanted into the left atrial appendage (Fig 4). The postoperative course was complicated with multiorgan failure leading to death 18 days after the pneumonectomy.

Comment

Early acute right heart failure after pneumonectomy is an uncommon, potentially fatal complication. The causes include massive pulmonary thromboembolism, cardiac herniation and torsion through a pericardial defect, massive acute myocardial infarction, and fluid overload. Our case is noteworthy in that the acute right heart failure that developed after right pneumonectomy was caused by a major left to right shunt through a previously unsuspected contralateral partial anomalous pulmonary vein.

Isolated partial anomalous pulmonary venous drainage from a pulmonary lobe is uncommon [1, 2] (usually occurring as part of a mixed type of total anomalous pulmonary venous drainage), and in most situations not physiologically important. The insignificant degree of left to right shunt (equal to or less than 25% of the cardiac output), and the absence of pulmonary hypertension,

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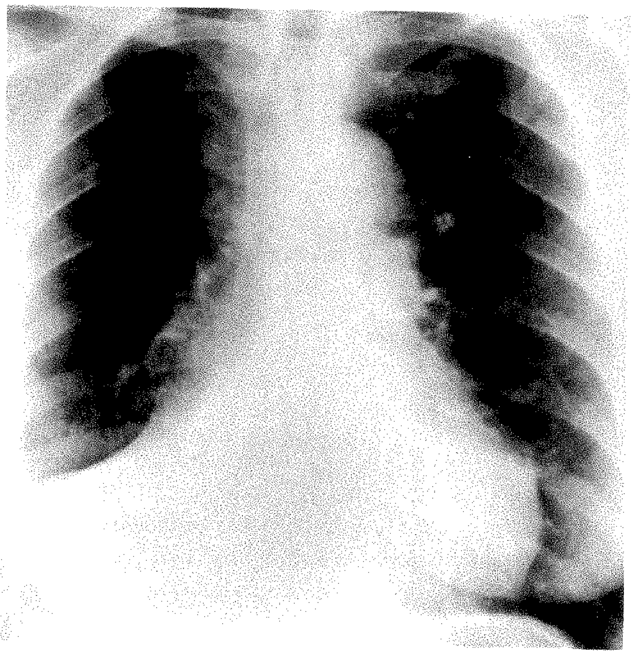

Fig 1. Chest radiograph on admission showing atelectasis of the right middle and lower lobes of the lung.

allows such an isolated anomaly to be compatible with normal life expectancy. Therefore, its importance has to be stressed with respect to contralateral pulmonary resection [3]. Isolated anomalous drainage of the left upper lobe vein to the innominate vein may be left uncorrected when found as part of a complex cardiac anomaly [4]. However, should the degree of left to right shunting increase to 50% of the cardiac output after right pneumonectomy, as it did in our case, then hemodynamic decompensation because of right ventricular overload could be expected to develop [5]. This situation would have been further aggravated if there was postoperative pulmonary hypertension because of either preexisting pulmonary vascular disease or restrictive communication between the anomalous connection and the innominate vein. According to Vlad (personal communication, July 18, 1990), a 2:1 low pressure or low volume shunt can usually be well tolerated in the pediatric population; therefore it can only be surmised that the patient's acute right ventricular failure was due to the combination of anesthesia, age, and occult cardiac disease when combined with the increased shunting through the anomalous vein after pneumonectomy (50% of the cardiac output).

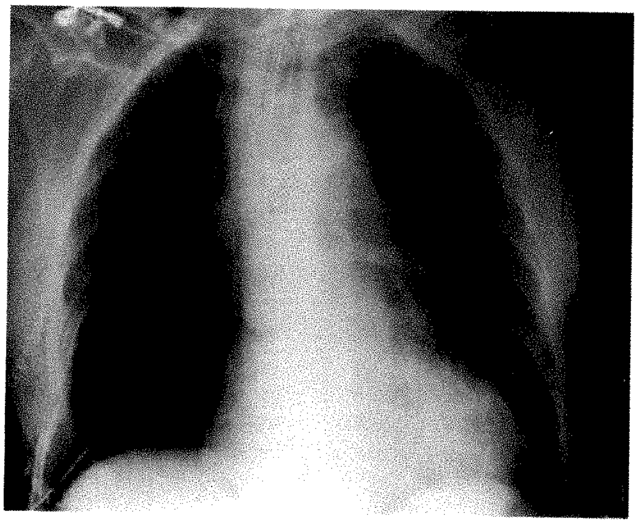

Fig 2. Chest radiograph performed in the immediate postoperative period with the patient intubated and supine. Note the normal position of the mediastinum.

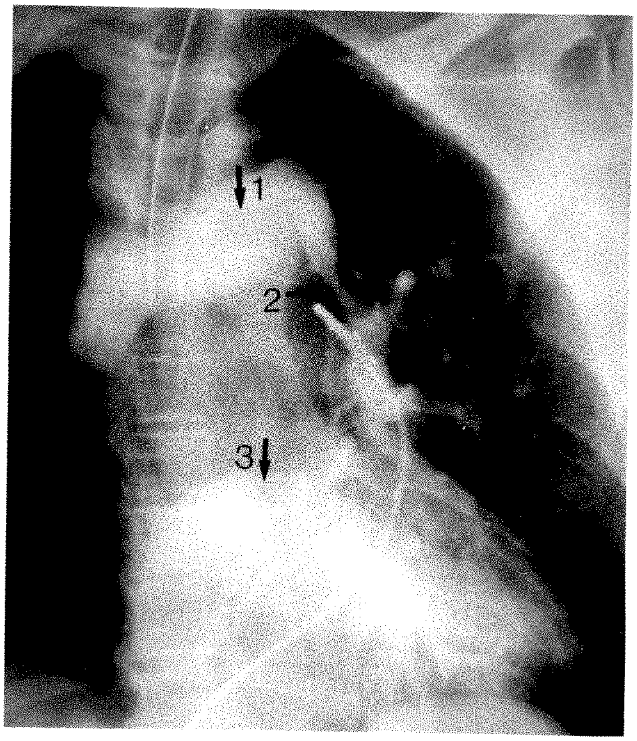

Fig 3. An emergency pulmonary angiogram (venous phase) reveals a major left to right shunt through a previously unsuspected partial anomalous pulmonary vein. Note the extremely dilated innominate vein (1), the anomalous left upper lobe vertical vein (remnant of the posterior cardinal vessel) (2), and the normal filling of the left atrium through the left inferior pulmonary vein (3).

The present case is of particular interest in that the left to right shunt associated with acute cardiac failure became manifest soon after the pulmonary resection. This is in contrast to the right to left cardiac shunt complicating pulmonary resection that develops slowly over a period of months and presents with dyspnea, central cyanosis, and signs of hypoxemia [6–9]. The diagnosis of either form of shunting (left to right, right to left) should be suspected by the presence of hemodynamic instability postoperatively and a lack of response to an inspired oxygen concentration of 1.00, and supported by a major change in the oxygen content from the expected on testing the right ventricular oxygen concentration by a pulmonary thermodilution catheter. Confirmation should be performed by cardiac catheterization with careful attention to the venous phase (as illustrated in this case), and early

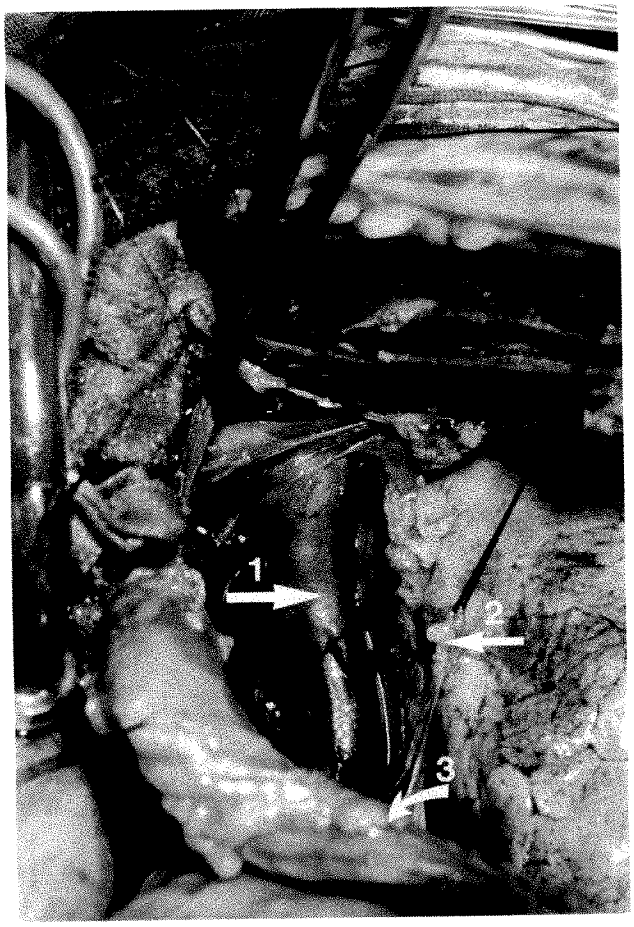

Fig 4. Intraoperative photograph displaying the anomalous superior pulmonary vein (1) and subsequent reimplantation through a parietal pleural (2) and pericardial (3) defect into the left atrial appendage.

definitive surgical correction must be attempted. In retrospect, the preoperative computed tomographic scan of the chest had revealed the presence of a vein close to the left mediastinum, but its surgical importance was not appreciated by the radiologist. This came to light only when the pulmonary angiogram confirmed the left to right shunt from the anomalous vein. Therefore, with routine use of preoperative thoracic computed tomographic scan, a diligent search for anomalous vascular structures should always be performed.

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Surgical Laser Ablation of a Pediatric Idiopathic Ventricular Tachycardia

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A pediatric patient with medically refractory idiopathic ventricular tachycardia was successfully treated by surgical laser ablation. Application of laser on the normothermic beating heart enables continuous electrophysiological assessment. The histopathology of idiopathic ventricular tachycardia and the advantages of laser ablation are presented.

(Ann Thorac Surg 1992;53:692–3)

Idiopathic ventricular tachycardia (VT) is an uncommon arrhythmia that threatens mainly children and young adults. The majority of these patients can be controlled medically and rarely undergo surgical treatment. We used surgical laser ablation in a pediatric patient because of medically refractory VT and associated heart failure.

A 1-year-old boy had grown up uneventfully until he was admitted to Nippon Medical School because of poor food acceptance and restlessness. His electrocardiogram showed sustained VT at a rate of 180 beats/min with QRS morphology, right bundle-branch block, and left axis deviation. His chest roentgenogram showed moderate cardiomegaly and pulmonary congestion. Two-dimensional echocardiography and left ventriculography showed no organic heart disease except for the reduced wall motion of the left ventricular apex. Ventricular tachycardia was reproducibly initiated and terminated by programmed electrical stimulation during electrophysiological study. Endocardial catheter mapping during VT revealed the earliest activation site at the inferior apex of the left ventricle. Rapid pacing from the right ventricular apex during VT demonstrated transient entrainment of VT. Thus, the mechanism of VT was considered to be reentry. Antiarrhythmic drugs, including lidocaine, disopyramide, flecainide, verapamil, and propranolol, were administered but none of them were assessed as clinically effective. Verapamil slowed the heart rate of VT but failed to terminate VT. The patient was placed on a regimen of a large dose of procainamide, 50 mg/kg daily, because of its prophylactic effect for the VT. However, when the patient reached the age of 2 years, sustained VT recurred frequently with symptomatic heart failure. The patient's lupus erythematosus test and antinuclear titer became positive, probably due to the procainamide. Therefore, the decision was made to attempt a nonpharmacological alternative to medical therapy. Initial electrical catheter ablation was attempted on December 19, 1988, but failed to ablate VT.

Operation was performed on March 22, 1989. The heart was exposed through a median sternotomy and appeared normal. Epicardial activation mapping during VT showed that the VT propagated from the inferior apex of the left ventricle. After the institution of normothermic cardiopulmonary bypass, aortic cross-clamping was performed and the coronary arteries were perfused through a separately cannulated tube in the proximal ascending aorta at a flow rate of 100 to 150 mL/min. This technique allowed a left ventriculotomy in the beating heart without the risk of systemic air embolism. Octopolar electrode mapping of endocardial activation during VT demonstrated earliest activation at the endocardial inferior apex of the left ventricle, preceding onset of QRS by 30 milliseconds (Fig 1). Abnormal trabeculae were observed adjacent to the earliest activation site, within the confines of the left ventricular apex. These were resected for pathological examination. The remainder of the endocardium, including the site of earliest activation, appeared normal. The continuous-wave neodymium:yttrium-aluminum garnet laser (wavelength, 1.064 μm) was chosen for the laser source. Each output was 20 W for 5 seconds, and the accumulated energy amounted to 500 J. Endocardial laser irradiation was attempted five times at the earliest activation site. Ventricular tachycardia was no longer inducible by programmed electrical stimulation despite the administration of isoproterenol. Additional cryosurgeries were performed at the earliest activation site to ensure the eradication of VT. The patient was weaned from cardiopulmonary bypass without inotropic support, and the postoperative course was uneventful. Pathological examination of the abnormal trabeculae showed focal endocardial thickening with increased fibroelastic tissue, compatible with the finding of endocardial fibroelastosis (Fig 2). Findings such as cardiac tumor were not seen. Three months postoperatively, electrophysiologic study was performed again and VT was not inducible by programmed electrical stimulation.

Comment

The clinical and electrophysiological characteristics of this patient coincided closely with descriptions reported previously [1, 2]. Other investigators [3, 4] described histologic evidence of myocarditis or dilated cardiomyopathy

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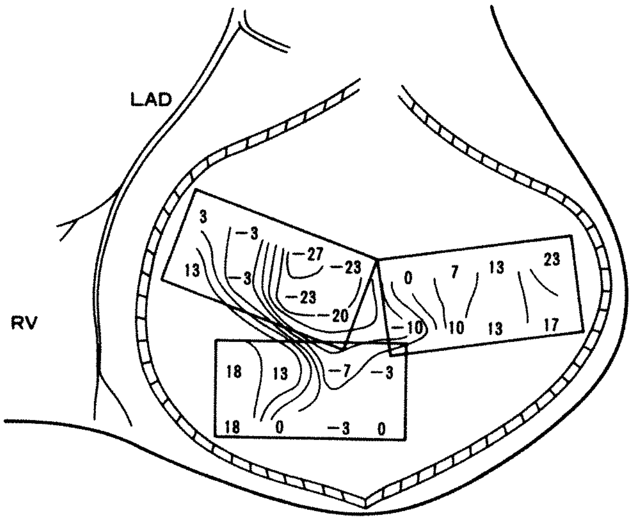

Fig 1. Endocardial activation mapping during ventricular tachycardia demonstrates the earliest activation site at the inferior apex of the left ventricle. (LAD = *left anterior descending coronary artery;* RV = *right ventricle.)*

in endomyocardial biopsy specimens of patients with idiopathic VT. Although the preoperative clinical evaluation showed no apparent cardiac structural abnormalities in this patient, abnormal trabeculae were observed adjacent to the earliest activation site and pathological examination showed findings compatible with endocardial fibroelastosis. Ventricular tachycardia was not terminated by resection of these abnormal trabeculae. Therefore, it was concluded that these abnormalities were not related to the arrhythmia mechanism, but were pathological consequences of sustained VT for a long period of time.

Several surgical procedures have been advocated for treatment of patients with idiopathic VT [5, 6]. A simple ventriculotomy may interrupt the reentry circuit [5]. However, the earliest activation site of VT is frequently located in the inferolateral left ventricle, and the left posterior fascicle may be responsible for the VT. A left ventriculotomy in its inferior portion is accompanied by potential risks, such as poor visualization and difficulty in hemostasis. The left ventriculotomy was applied in its apical portion in this patient to avoid these risks. Moreover, the left ventriculotomy was placed under the separated coronary perfusion with aortic cross-clamping. This technique enabled safe endocardial mapping during VT without the risk of systemic air embolism.

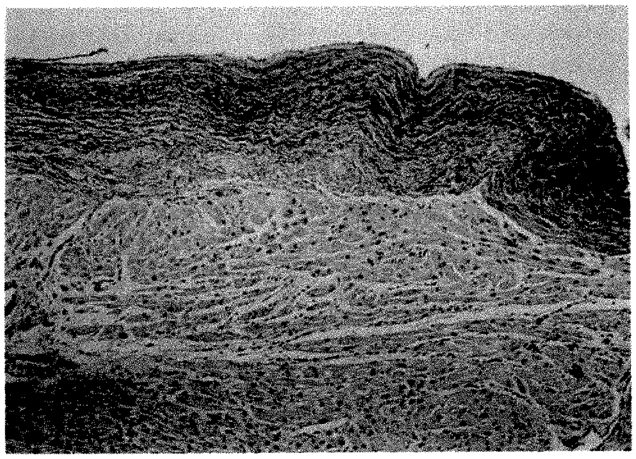

Fig 2. Light micrograph of the abnormal trabeculae shows endocardial thickening with increased fibroelastic tissue. (Elastica van Gieson stain; ×100 before 52% reduction.)

Surgical laser ablation of VT was successfully performed in this patient. Transmural mapping of the VT was not performed, so the possibility cannot be excluded that transmural reentry or intramural origin is responsible for the VT in this patient. Therefore, an ablation technique, such as laser irradiation, that could produce coagulation necrosis of reliable depth in the normothermic myocardium was necessary [7]. We have observed that the depth of coagulation necrosis could be regulated precisely by the energy density (J/cm^2) of neodymium: yttrium-aluminum garnet laser irradiation in normothermic canine endocardium. Therefore, we adopted the neodymium:yttrium-aluminum garnet laser as a means of ablation because of its reliable effects on the normothermic myocardium as compared with cryoablation. Moreover, laser ablation can be performed under continuous electrophysiological assessment, including cardiac mapping, in the normothermic beating heart. In contrast, cryoablation usually requires cardioplegic arrest, which makes this assessment impracticable. Although additional cryosurgeries were used in this patient, we believed that the laser irradiation eradicated the VT, because the VT was no longer induced by the programmed electrical stimulation after the laser ablation.

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Transaortic Patch Angioplasty for Left Coronary Ostial Stenosis in a Patient With Takayasu's Aortitis

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A 35-year-old woman who had left coronary ostial stenosis and aortic valve regurgitation due to Takayasu's aortitis underwent transaortic patch enlargement of the stenosed left coronary ostium in combination with aortic valve replacement. This technique may be suitable and recommendable as an alternative to aortocoronary bypass grafting or endarterectomy for coronary ostial stenosis in Takayasu's aortitis.

(Ann Thorac Surg 1992;53:694–6)

Takayasu's aortitis is an inflammatory disorder of the aorta with unknown specific etiology, and the fibrous intimal proliferation produces narrowing or obstruction of main branches of the aorta, including coronary artery ostia. The aortic valve is also not infrequently involved. The presence of coronary ostial stenosis is potentially lethal in Takayasu's aortitis. Aortocoronary bypass grafting or transaortic endarterectomy for this serious complication has been reported previously. However, the late results of these procedures have been unsatisfactory because of the inflammatory process of the disease.

To prevent the late proximal occlusion of bypass graft or recurrent stenosis after endarterectomy, transaortic patch enlargement of the stenosed left coronary ostium was performed in combination with aortic valve replacement in a patient with Takayasu's aortitis.

A 35-year-old woman was referred to our hospital because of cardiomegaly and absence of left radial pulse. She had complained of exertional dyspnea with palpitation and chest pain 2 years before admission. On examination, a diastolic decrescendo murmur was audible along the left sternal border and a bruit, on the right carotid artery. The blood pressure was 170/0 mm Hg in the right upper extremity, but the left radial pulse was not palpable. At cardiac catherterization in March 1991, aortography showed severe aortic regurgitation and coronary angiography revealed a 75% stenosis of the left coronary ostium and normal right coronary artery (Fig 1A). Left ventriculography showed depressed left ventricular function with a left ventricular end-systolic volume index of 111 mL/m^2 and an ejection fraction of 0.45. Aortography revealed total occlusion of the left carotid, left subclavian, and left vertebral arteries.

The operative procedure is shown in Figure 2. Standard cardiopulmonary bypass was used with moderate hypothermia. Retrograde perfusion of crystalloid cardioplegic solution was introduced for myocardial protection. The aorta was incised transversely, and the incision was extended across the left lateral wall toward the left coronary ostium. The aortic wall showed severe fibrous thickening (4 to 5 mm in width). The aortic valve was fibrously thickened with poor coaptation. The left coronary ostium was stenotic (2 mm in diameter) with severe intimal thickening. After the aortic valve was removed, the stenosed coronary ostium was incised toward the left main coronary artery trunk for a length of 10 mm. The intima of the left main coronary artery was intact. The ostia was enlarged with a 0.6% glutaraldehyde-treated autologous pericardial onlay patch (teardrop-shaped, 35 mm in length and 15 mm in maximum width). The patch was sutured to the left main coronary artery with 6-0 monofilament and was continuously sutured up to the aortic wall with 4-0 monofilament. After the ostium was constructed, a Björk-Shiley monostrut valve (No. 23) was implanted with interrupted sutures. The patient was weaned from cardiopulmonary bypass uneventfully.

Histologic sections of the ascending aortic wall demonstrated marked intimal proliferation and fibrous degeneration of the elastic fibers of the media and adventitia with round cell infiltration.

The postoperative course was uneventful, and the patient was discharged 29 days after operation. Postoperative coronary arteriography in June 1991 showed widely enlarged ostium of the left coronary (Fig 1B).

Comment

Takayasu's aortitis has an unknown specific etiology and predominantly affects young women. The disease has an unpredictable course, showing slow progression. The basic pathological process is that of marked intimal proliferation and fibrous scarring of the media and adventitia.

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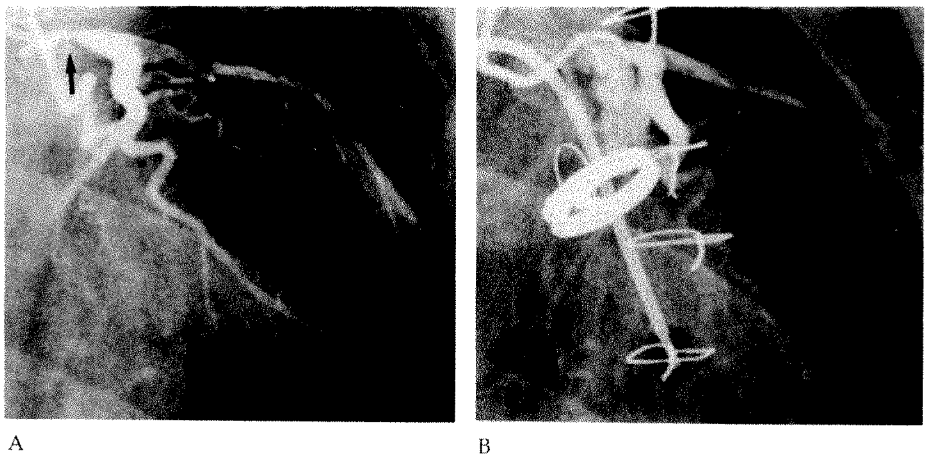

Fig 1. (A) Preoperative coronary angiogram in a right anterior oblique projection shows 75% stenosis in the left coronary ostium (arrow). *(B) Postoperatively, the widely enlarged ostium of the left coronary artery is demonstrated.*

Morbidity and mortality depend on the presence or absence of severe complications caused by stenosis or occlusion of major branches of the aorta, aortic regurgitation, and coronary ostial stenosis. Coronary ostial stenosis is considered a not infrequent and potentially fatal complication of Takayasu's aortitis. Coronary artery diseases are characteristically limited to the coronary ostia or the proximal segment of the coronary artery.

Aortocoronary bypass grafting or transaortic endarterectomy has been reported previously to deal with coronary ostial stenosis in Takayasu's aortitis [1–6]. To our knowledge, 13 patients having coronary ostial stenosis associated with aortic regurgitation have been reported to have simultaneous aortocoronary bypass grafting or endarterectomy and aortic valve replacement. However, the late results of aortocoronary bypass grafting have not been satisfactory. Ohara and colleagues [4] reported a low graft patency rate (50%) in their 6 patients undergoing aortocoronary bypass grafting. Cippiano and colleagues [2] stated that it was difficult to construct proximal anastomoses of the grafts because of extremely thickened aortic wall, and inflammation of the aortic wall may have contributed to the late proximal occlusion of bypass grafts. Internal mammary artery or gastroepiploic artery cannot or should not be used because of potential stenosis or occlusion of branches of the aorta in this disease. Endarterectomy may be unreliable to reconstruct the stenosed coronary ostium and, moreover, recurrent stenosis may occur with the inflammatory process of the disease. Therefore, extended patch enlargement of the stenosed coronary ostium may be more efficacious and may provide more favorable late results, in that a large patch of pericardium may prevent recurrent stenosis of the coronary ostium postoperatively. In 1987, Morgan and colleagues [6] reported a successful case of patch enlargement of the right coronary ostium in Takayasu's aortitis. Our patient may be the second such case. A glutaraldehyde-treated autologous pericardial patch was used in our patient to prevent possible late shrinkage of the pericardium.

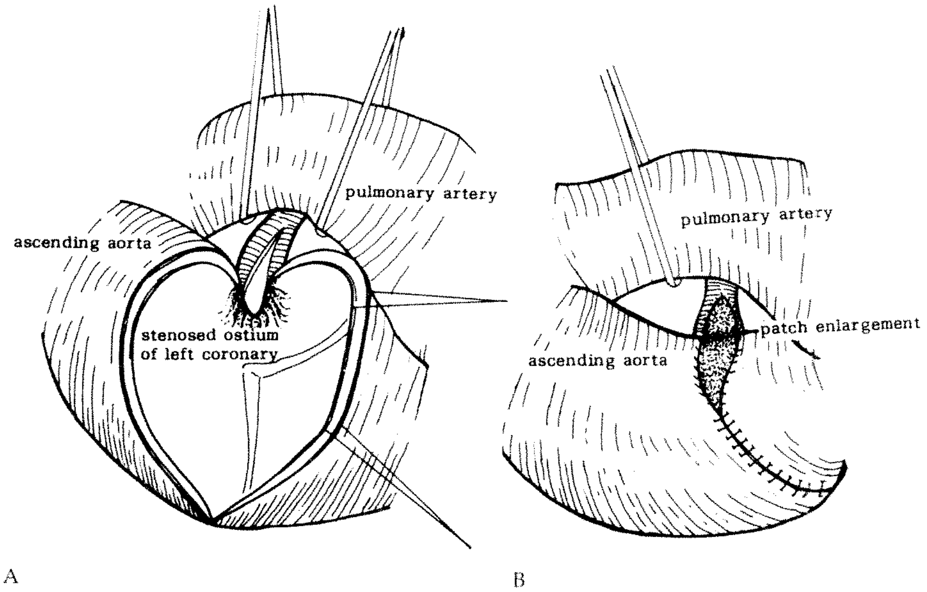

Fig 2. Operative technique: an incision of the aorta was extended across the left aortic wall toward the left coronary ostium and the stenosed ostium was incised toward the left main coronary artery trunk 10 mm in length after the aortic valve was removed (A). The left coronary ostium and main trunk were enlarged with a 0.6% glutaraldehyde-treated autologous pericardial patch (B).

The transaortic patch angioplasty we used is that described by Hitchcock and colleagues [7]. Recently, Dion and colleagues [8] reported 22 selected patients undergoing transaortic patch angioplasty of the left main coronary artery, though not in the management of Takayasu's aortitis. Their excellent results encouraged us to attempt this technique, even though it may be difficult to approach the left main coronary trunk in Takayasu's aortitis because of a scarring fibrous adhesion between the ascending aorta and the pulmonary artery.

Although our experience is limited and the long-term result is needed for final judgment, we believe that transaortic patch angioplasty is warranted as an alternative to aortocoronary bypass grafting or endarterectomy for coronary ostial stenosis in Takayasu's aortitis.

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Intrapleural Rupture of the Azygos Vein

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Intrapleural rupture of the azygos vein associated with hypovolemic shock resulting from blunt chest trauma is reported. Management demanded an emergency department right thoracotomy with venous ligation. Aortography to rule out associated arterial injury was performed. The previously published 7 cases of azygos vein rupture are reviewed as are possible etiologic mechanisms responsible for this rare injury. The history and clinical signs compatible with this injury are emphasized.

(Ann Thorac Surg 1992;53:697–9)

Blunt trauma resulting in isolated azygos vein disruption is rare but potentially fatal. The lethal nature of cardiac and great vessel injury has been well described [1]. Few descriptions of isolated mediastinal venous injuries exist. A case of blunt chest trauma with right hemothorax and shock resulting from an isolated azygos venous arch disruption is presented. A review of the literature is discussed along with possible etiologic mechanisms based on the anatomy of the azygos system.

A healthy 19-year-old man was involved in a single vehicle automobile accident as an unrestrained front seat passenger. Impact with a stationary object occurred at approximately 50 mph. Once extricated, the patient was noted to be unconscious with a systolic blood pressure of 60 mm Hg and heart rate of 160 beats/min. Military antishock trousers were applied and intravenous resuscitation was initiated before transport of the patient to our emergency department. Initial survey of the patient upon arrival to our emergency department showed an inebriated, combative man with a heart rate of 160 beats/min and blood pressure of 140/60 mm Hg (military antishock trousers inflated). His airway was adequate. A right supraorbital laceration, several abrasions over the right anterolateral chest, and a right ankle dislocation were noted.

Auscultation of the chest demonstrated mildly diminished breath sounds bilaterally with no crepitus or chest wall deformity noted on palpation. The abdomen was mildly distended. Crystalloid resuscitation was continued. A portable chest radiogram showed a large right hemothorax (Fig 1). Right tube thoracostomy was performed and the tube clamped after approximately 1,500 mL of blood was removed. Due to sustained hypotension despite ongoing crystalloid and blood resuscitation, an emergency department right thoracotomy was performed through the fifth intercostal space. Brisk bleeding was noted in the superior mediastinum, which was easily controlled with laparotomy packs while blood volume and hemodynamic stability were restored. The patient was then transferred to the operating room, where exploration revealed disruption of the midportion of the azygos venous arch. Both proximal and distal ends were suture-ligated. Diagnostic peritoneal lavage was performed; the results were negative. A postoperative arch aortogram was obtained to rule out associated arterial injury. Facial lacerations were repaired, and the right ankle dislocation was reduced and casted. Our patient went on to have an uneventful postoperative recovery and was discharged on postoperative day 8.

Comment

As noted in Table 1, there have been 7 previous case reports of azygos vein injury resulting from blunt chest trauma. Each resulted from a motor vehicle accident involving a deceleration force. Clinical presentation includes shock with hemorrhage into the right pleural space. Right hemothorax is the most common finding on chest radiogram. A wide mediastinum or vertebral injury may be present as well. Detailed review of the case histories indicates frequent confusion regarding the cause of the hypovolemic shock in these patients. Associated multisystem injuries often complicate the clinical picture. Therapy demands right thoracotomy with ligation or repair of the vessel. There appears to be no morbidity associated with the former approach, and it is the most commonly employed method of treatment. Because of possible associated great vessel injury, arch aortography is imperative [4].

Anatomically, the azygos vein is positioned in the posterior mediastinum and is invested within the parietal pleura. Receiving the right intercostal veins, the azygos vein is "tethered" posteriorly. Passing posterior to the descending aorta and thoracic duct in the left hemithorax, the hemiazygos vein courses horizontally across the vertebral column to terminate in the azygos vein. Taking an anterosuperior direction, the azygos arch passes over the right pulmonary hilum to enter the superior vena cava proximal to its investment by the pericardium.

Attempting to explain the possible etiologic mechanism of venous disruption, Spagliardi and Polombo [2] and Snyder and Eyer [7] proposed that the injury to the

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The opinions expressed are those of the authors and do not reflect the opinions of the United States Air Force or the Department of Defense.

azygos vein was caused by an axial/rotation force placed on the venous arch. Such a force would result from sudden deceleration. Conceivably, the aortic outflow tract and superior vena cava–inferior vena cava entrance into the right atrium would act as a pivot point around which the decelerating cardiac mass would rotate in an anteromedial direction. An axial stretch of the azygos arch results from it being relatively fixed posteriorly by the intercostal tributaries while being pulled forward by the more mobile superior vena cava. This is depicted in Figure 2.

Reporting an additional case of isolated disruption of the azygos vein, Salizzoni and associates [3] went on to describe venous arch disruption associated with anterior displacement of the T-5 vertebral body. They presented as two possible causes direct vein injury by the subluxed/fractured vertebral body and a sudden increase in venous pressure rupturing the vein. Such increases in venous pressure could result from compression of the cardiac mass between the sternum and vertebral column or from compression of the peritoneal cavity, or both.

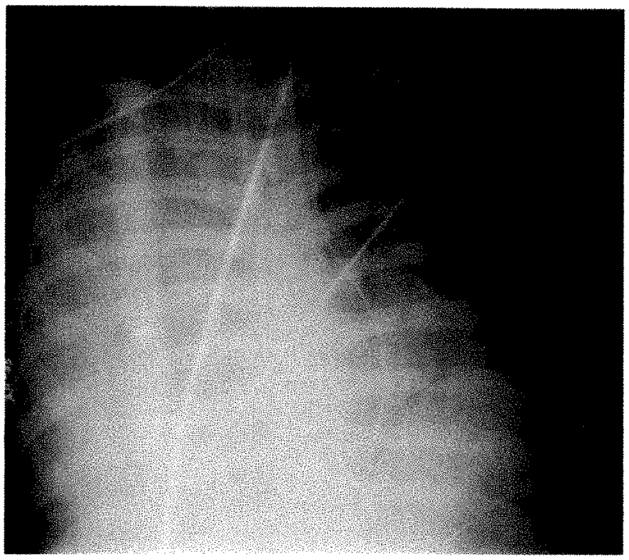

Fig 1. Emergency department chest radiogram demonstrating right hemothorax.

Table 1

First Author (year)	Patient No.	Presentation	Radiogram	Operative Findings	Associated Injuries	Survival
Spagliardi [2] (1978)	1	Shock	Right hemothorax	Laceration of azygos vein at SVC junction	Liver laceration	Yes
Salizzoni [3] (1980)	2	Shock	Right hemothorax	Rupture of azygos arch, intercostal vessel tear	Liver laceration	Yes
	3	Shock	Right hemothorax	Near-total avulsion of azygos vein at SVC junction	T-5 fracture dislocation, rib fractures, lower extremity fracture	No
Baldwin [4] (1984)	4	Shock	Wide mediastinum	Avulsion of azygos vein at SVC	Pelvic, right clavicle, lower extremity fractures, right subclavian disruption	Yes
Sherani [5] (1986)	5	Shock	Right hemothorax	Complete transection of azygos vein	Hepatic laceration, closed head trauma, lower extremity fracture	Yes
Coates [6] (1987)	6	Shock	Right hemothorax	Partial tear of azygos–SVC junction, pelvic fracture, bladder injury, intracerebral hematoma	Multiple rib fractures, right clavicle fracture	Yes
Snyder [7] (1989)	7	Shock	Early opacification of right hemidiaphragm, late large hemothorax	Complete transection of azygos arch	Left rib fractures, lumbar vein injury	Yes
Thurman (1992)	8	Shock	Right hemothorax	Rupture azygos arch	Closed head trauma, right ankle dislocation, facial lacerations	Yes

SVC = superior vena cava.

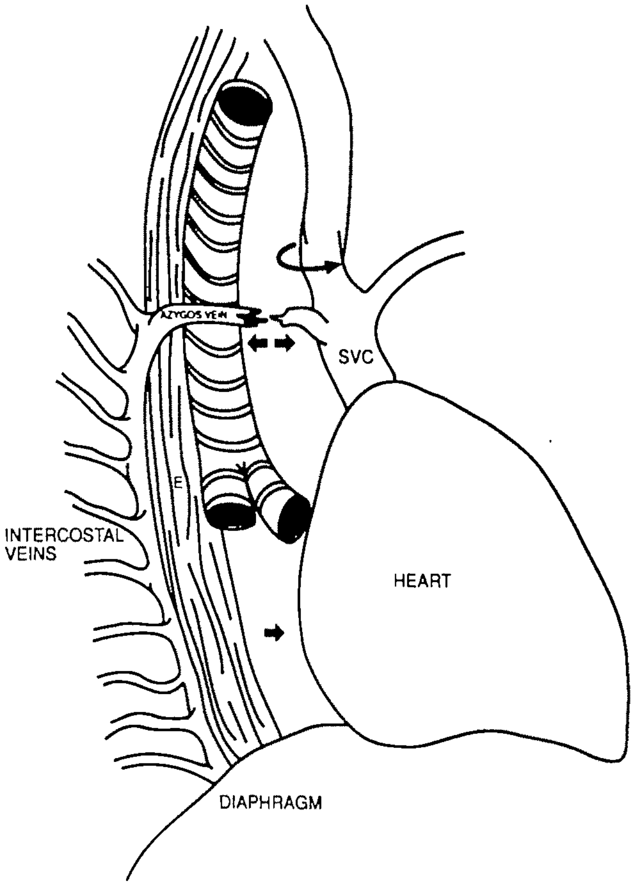

Fig 2. During sudden deceleration, anterior displacement of the mobile heart and superior vena cava (SVC) *imposes a stretch and shear force on the azygos arch, which is tethered posteriorly by the intercostal veins. The result is arch disruption.* (E = *esophagus.)*

Owing to low pressure venous characteristics and investment within an intact mediastinal pleura, an isolated, contained tear of the azygos venous system would remain clinically silent. Once assured by an arteriogram there is no arterial injury, one is less concerned with the "wide mediastinum" associated with blunt chest trauma. Whether contained azygos vein disruption is a common cause of widened mediastinum is uncertain. Perhaps a closer assessment of the azygos system during autopsies performed on victims of blunt thoracic trauma would reveal a higher incidence of this injury.

The potentially lethal nature of intrapleural rupture of the azygos system is presented. The mechanism associated with the 8 reported cases of azygos vein disruption was blunt thoracic trauma resulting from a deceleration-type injury involving automobiles. Pertinent history and clinical signs that should raise one's index of suspicion for this type of injury are as follows:

1. Deceleration force
2. Unrestrained automobile passenger
3. Shock on arrival to emergency department
4. Obvious signs of blunt chest trauma
5. Diminished right breath sounds
6. Right hemothorax on chest radiogram
7. Upper thoracic spine fracture/dislocation
8. High right tube thoracostomy output

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Heart and Unilateral Lung Transplantation for Cardiomyopathy With High Pulmonary Vascular Resistance

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Heart and left lung (en bloc) transplantation was used as an approach to end-stage cardiomyopathy with very high pulmonary vascular resistance. This surgical method was applied to a 13-year-old girl who did very well initially, but died 5 months later of severe pulmonary and cardiac rejection. The pulmonary perfusion scintigraphy showed equalization of the blood flow in both lungs after 42 days, and complete reversal of the pulmonary vascular changes in the opposite lung was observed at autopsy.

(Ann Thorac Surg 1992;53:700–2)

High pulmonary vascular resistance (PVR) after end-stage cardiomyopathy has been a contraindication to heart transplantation [1]. The advent of clinically successful heart-lung transplantation, initiated by Reitz and associates [2] at Stanford University in 1980, has brought new hopes to that group of patients. Nevertheless, the long-term results have been limited by a high incidence of chronic pulmonary complications, particularly, obliterative bronchiolitis [3]. Heart and unilateral lung transplantation has been successfully applied to patients with primary pulmonary disease, cor pulmonale, and extensive unilateral pleural adhesions by Kawaguchi and coworkers [4]. They aimed to avoid bleeding problems. We are reporting this technique as an approach to patients with end-stage cardiomyopathy and very high PVR.

A 13-year-old girl was referred to us for heart transplantation. She had had symptoms of heart failure since the age of 2 years, when dilated cardiomyopathy was diagnosed. The symptoms progressed to functional class IV (New York Heart Association), and she became physically very limited; she was often in the hospital, and required repeated intensive care unit admissions in the last 6 months. Cardiac catheterization on December 13, 1989, showed very elevated pulmonary artery pressure and a calculated PVR index of 15.6 Wood units/m^2, with the patient wearing an oxygen mask (Table 1). Her two-dimensional echocardiogram demonstrated overall dilatation of the heart and diffuse hypokinesia of both ventricles, with a left ventricle ejection fraction of 0.18. This very high PVR contraindicated orthotopic heart transplantation, and she was placed in our heart-lung transplantation program. On June 12, 1990, we had a 19-year-old donor who was ABO compatible but whose chest dimensions were about 30% larger than hers. To overcome this, and having in mind the possible reversion of the pulmonary vascular alterations in the opposite lung, we decided to perform heart and single-lung transplantation. This was explained to her parents, who consented to the procedure.

The operation was performed on June 12, 1990. With the donor next door to the recipient, the heart-lung block was removed from the donor using cardiopulmonary bypass and systemic hypothermia. The graft preparation was completed by right lung resection. The recipient, after median sternotomy, was placed on cardiopulmonary bypass by ascending aorta and bicaval cannulation. On hypothermia (25°C), the heart and left lung were excised. The left main bronchus and the pulmonary artery were divided. The right pulmonary veins were kept with a small left atrial cuff. The graft was implanted by suturing the left main bronchus, the right pulmonary artery, and the right pulmonary veins with atrial cuff to the left atrium, followed by aortic and bicaval anastomosis. The left bronchial anastomosis was covered by the recipient peribronchial tissue, which was left in excess, to protect it from dehiscence. Microscopic examination of the recipient's excised lung (Fig 1A) showed hypertrophy of the muscular arteries and mild intimal hyperplasia. The elastic arteries showed parallel elastic fibers. These grade II vascular alterations (Heath-Edwards classification) were consistent with the preoperative heart catheterization findings. Cyclosporine, azathioprine, and prednisone were given as immunosuppressive therapy.

The postoperative course was complicated by left bronchial clot obstruction on the first postoperative day (POD) and left pulmonary acute rejection on POD 6. These problems were overcome with proper treatment. The

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Table 1. Preoperative and Postoperative Catheterization Data

Variable	Preoperative	POD 42
PAP (mm Hg)		
Systolic	65	23
Diastolic	45	9
Mean	52	14
Wedge	17	9
Mean AoP (mm Hg)	76	85
Mean RAP (mm Hg)	14	6
Cardiac index (L · min^{-1} · m^{-2})	2.24	3.6
PVR index (Wood units/m^2)	15.6	1.4

AoP = aortic pressure; PAP = pulmonary artery pressure; POD = postoperative day; PVR = pulmonary vascular resistance; RAP = right atrial pressure.

patient was extubated on POD 2, transferred from the intensive care unit on POD 4, and discharged from the hospital on POD 23. Readmitted on POD 42 for routine evaluation, she was clinically very well with good cardiorespiratory function. The technetium pulmonary perfusion scintigraphy and pulmonary angiography showed equal right and left pulmonary perfusion, indicating a well-balanced PVR. The heart catheterization data (see Table 1) indicated a major decrease in pulmonary artery pressure and PVR. The chest radiogram (Fig 2B) showed good appearance of the left lung and some increase in the right lung vascularity. These findings were consistent with early reversion of right lung high vascular resistance.

The patient was hospitalized again on November 16, 1990, with fever, mild dyspnea, and yellowish sputum. The chest radiogram showed a left lung infiltrate more intense in the lower lobe, and she was treated with antibiotics that night. The next day transbronchial lung biopsy showed acute pulmonary rejection, and treatment with methylprednisolone (15 mg · kg^{-1} · d^{-1}) was begun. Two days later the left pulmonary infiltrate partially regressed, but frank heart failure developed. The left ventricle ejection fraction dropped from 0.65 to 0.39, and the endomyocardial biopsy showed severe acute rejection. OKT3 was added to the treatment, but she died 5 days later of intractable heart failure. The autopsy confirmed the cardiopulmonary rejection and showed complete regression of the vascular alterations in the right lung (Fig 1B)

Comment

The reversibility of pulmonary hyperresistance secondary to passive pulmonary venous hypertension after heart transplantation is a proven fact, even in patients in advanced stage in whom heterotopic heart transplantation was indicated [1, 5]. Isolated heart transplantation of even an oversized heart would carry a very high risk when applied to a patient like ours. The unadapted right ventricle would fail when submitted to such a high PVR. This acute right ventricular failure is, generally, followed by cardiogenic shock and early death [1]. The use of a special heart donated from a recipient of heart-lung transplantation (domino procedure) would be appropriate [6], but we believe that this procedure is not preferable to the donor because the results of lung transplantation have improved [7]. Heterotopic heart transplantation, an alternative proposed by Barnard and Losman [8] would be technically difficult to apply to our patient owing to the large size of her heart and the presence of cardiac arrhythmias, which would increase the risk of thromboembolism. These complications are serious limitations to the method [9]. Heart and double-lung transplantation would be, in our opinion, an overdimensioned approach to the prob-

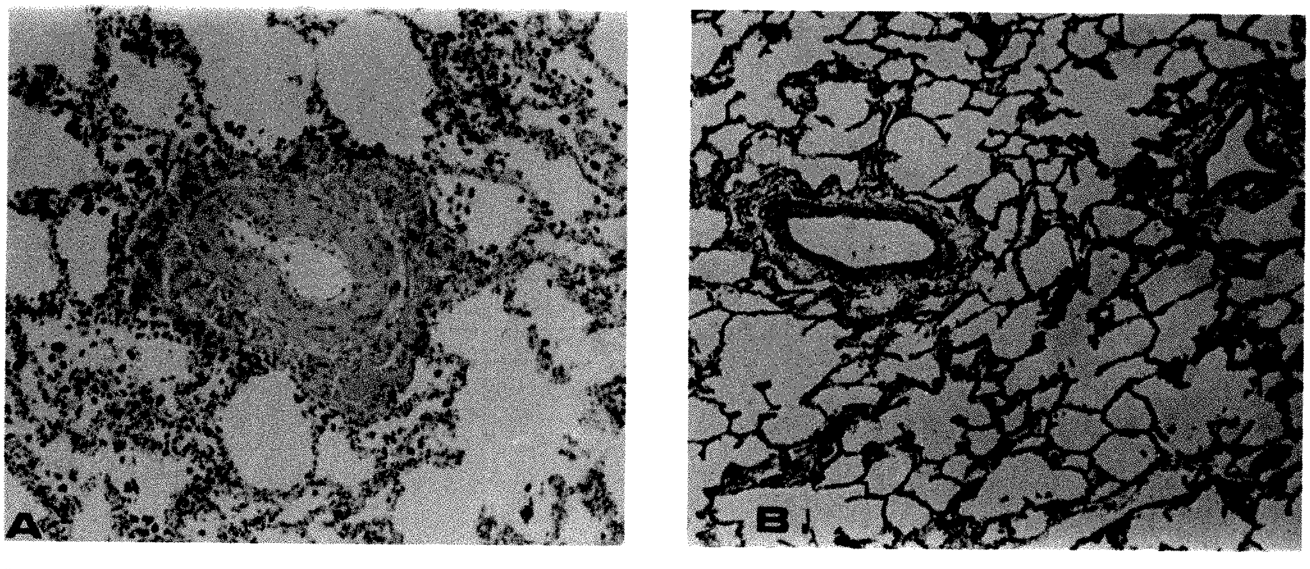

Fig 1. Photomicrographs of recipient's lungs: (A) left lung excised at operation, showing pulmonary vascular alterations of long-standing pulmonary hypertension; (B) right lung at autopsy, 159 days after heart and left lung transplantation, showing complete regression of vascular changes.

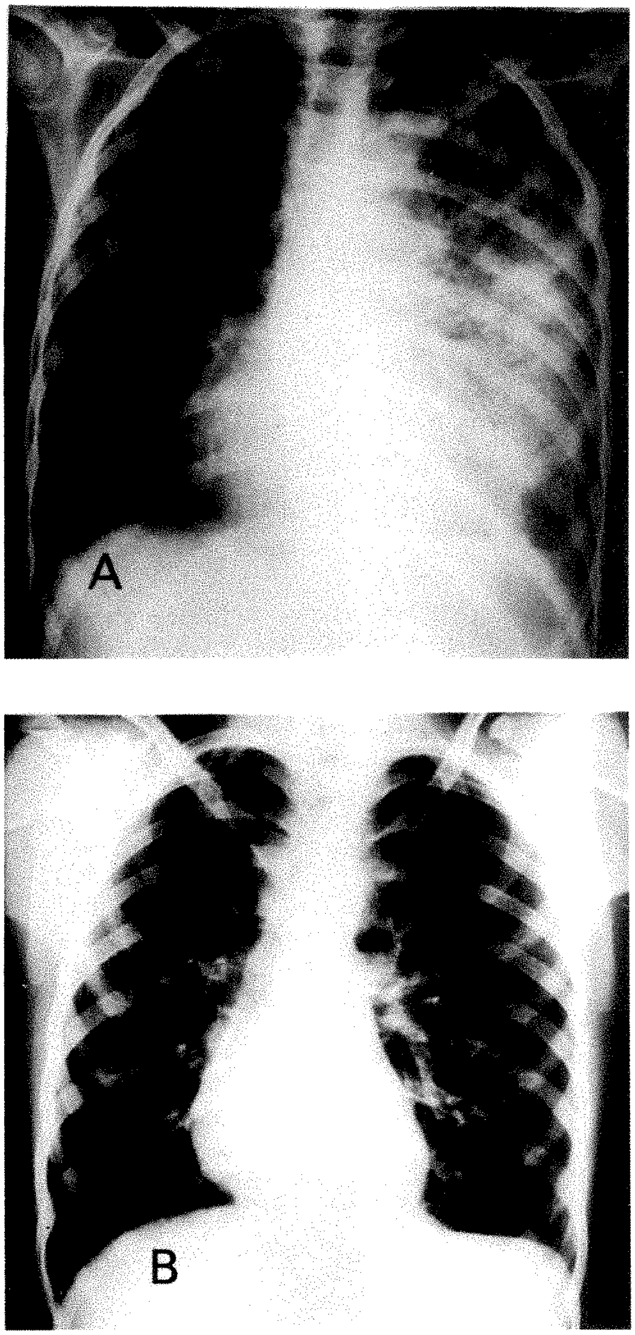

Fig 2. Chest radiographs showing (A) left lung parenchymal infiltration consistent with acute pulmonary rejection 6 days after operation and (B) good appearance of left lung and some increase in right pulmonary vascularity on the 42nd postoperative day.

lem, because we would be excising potentially normal lungs. The recovery of one lung could be of great importance to overcome the long-term pulmonary complications of heart-lung transplantation. Besides our distinct indication for heart and unilateral lung transplantation, our surgical technique is somewhat different from that described by Kawaguchi and associates [4]. Whereas they kept the recipient pulmonary artery trunk, which was connected to the donor pulmonary trunk, we anastomosed the right pulmonary artery directly. The latter technique seems to be simpler to us.

The PVR decrease in the remaining lung, shown by pulmonary scintigraphy and angiography and confirmed by microscopy, indicates that this phenomenon is a real possibility with this procedure. The resolution of high PVR, already observed after heterotopic and orthotopic heart transplantation [1, 5], may occur more rapidly after heart and unilateral lung transplantation because with this latter procedure the pulmonary pressure drops to normal immediately after the operation. In our opinion, continuous advances in immunotherapy to prevent allograft rejection and its acute and chronic consequences will make the early hemodynamics a very important component of the overall heart transplantation results. This stresses our alternative as an appropriate procedure, for select cases, because it is expected to have a lower risk of early hemodynamic problems that are seen with isolated heart transplantation.

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Cardiac Torsion After Lobectomy With Partial Pericardectomy

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Cardiac herniation and torsion after intrapericardial pneumonectomy without closure of the pericardium is widely recognized. However, such a complication occurring after lobectomy has been rarely discussed in the literature. We describe a case of cardiac torsion of late onset that developed in a woman who had undergone left upper lobectomy as part of a resection for a malignant thymoma.

(Ann Thorac Surg 1992;53:703–5)

Herniation of the heart with subsequent torsion is extremely rare, and fatal if unrecognized. The majority of cardiac herniations occur after surgically created defects in the pericardium, but 3 cases have been reported of cardiac herniations through congenital pericardial defects [1–3]. Blunt trauma to the chest may rupture the pericardial sac, allowing cardiac herniation to occur with subsequent torsion or entrapment within the edges of the pericardial defect [4]. The most widely recognized cause of cardiac torsion is intrapericardial pneumonectomy without closure of the pericardial defect. Although presenting in a similar manner to those cases of postpneumonectomy cardiac torsion, this case is unusual in the late development of torsion after operation.

A 45-year-old woman had a 3-year history of pain in the left side of her chest and dysphagia. She had no clinical signs and no evidence of myasthenia. A posteroanterior chest roentgenogram showed a left-sided mediastinal lesion, which appeared to be arising out of the anterior mediastinum on the lateral chest roentgenogram. Her full blood count, urea, electrolytes, and liver function tests were normal. A clinical diagnosis of thymoma was made, and she was admitted for median sternotomy. At median sternotomy a large lobulated mass was found protruding from the anterior mediastinum and between the upper and lower left lobes of the lung. It was involving the left phrenic nerve and pericardium. A piece of pericardium approximately 4 cm × 5 cm was resected superiorly in the midline, the pulmonary artery was exposed, and the phrenic nerve was sacrificed. It was not possible to dislocate the left upper lobe forward without precipitously dropping the blood pressure. The sternotomy was closed after leaving drains to the right pleura and mediastinum, and a left thoracotomy was performed. The left

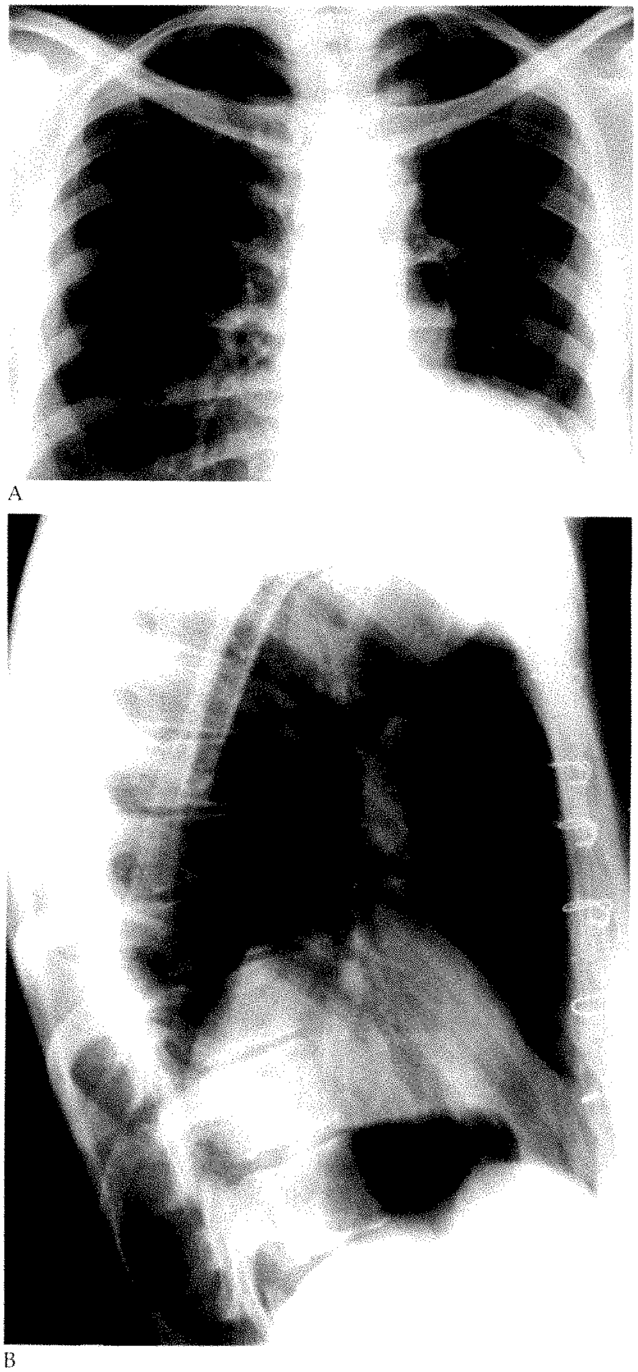

Fig 1. (A) Posteroanterior chest roentgenogram showing cardiac torsion. The normal left ventricular shadow has altered, with an acute angle between the mediastinum and left heart border. (B) Lateral chest roentgenogram showing cardiac torsion, with a shift of the heart shadow into a posterior position.

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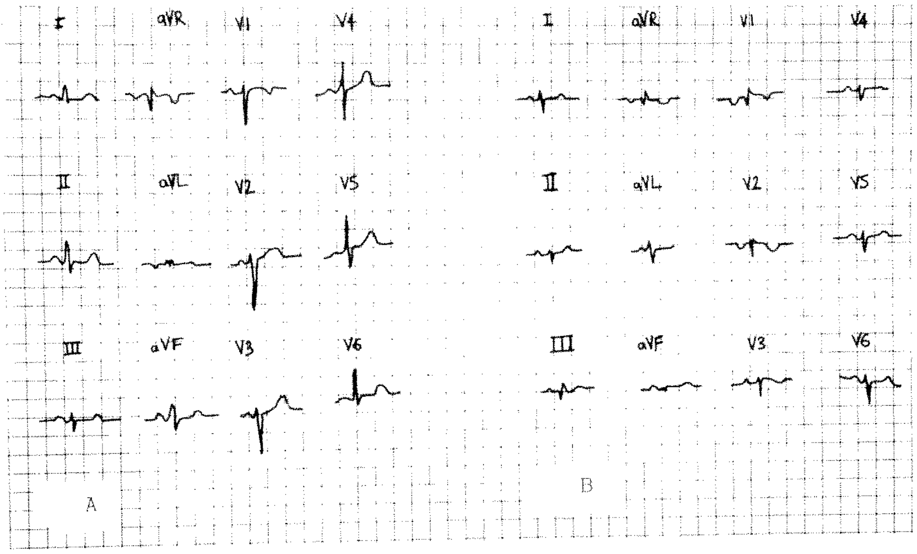

Fig 2. Electrocardiograms (A) after median sternotomy and resection of thymoma and (B) at presentation with cardiac torsion. Note small QRS complexes, Q waves in lead III, and inverted T waves in leads V_2 and V_3.

upper lobe was resected with attached thymic tumor. The pericardium was left widely open and intravenous digoxin administered. Histology of the resected tumor showed a malignant lymphoepithelial thymoma with invasion of the pericardium.

Her postoperative period was uncomplicated and she was discharged from the hospital 8 days postoperatively. However, 14 weeks after her operation she had increasing dyspnea. Her exercise tolerance had deteriorated from walking 1.5 miles to only one flight of stairs. She also complained of being able to feel her heart beating at the left side of her chest posteriorly. On examination she was not dyspneic at rest. Her peripheries were cool; the jugular venous pulse was not visible, blood pressure was 130/70 mm Hg, and pulse rate was 80 beats/min and regular. Heart sounds were normal, but the apex beat was displaced to the posterior axillary line. The carotid pulse was of lower volume than femoral pulsation. Chest expansion was reduced from previous examinations on the left side. Chest roentgenogram showed her heart shadow was displaced posteriorly on the lateral films (Fig 1). Electrocardiogram showed small voltage complexes with Q waves in lead III and inverted T waves in leads V_2 and V_3 (Fig 2). An echocardiogram showed a grossly displaced heart with the apex lying above the spleen. There was good left ventricular function, and no intracardiac abnormality.

Because of her deteriorating exercise tolerance and electrocardiographic findings, operative intervention was planned. Bronchoscopy showed a distorted left main bronchus, which was displaced posteriorly. A thoracotomy through the scar of the previous left thoracotomy was made. The heart was found displaced posteriorly into the left costophrenic recess, and adherent to the chest wall and diaphragm by adhesions. Nodules were also found on the diaphragm and chest wall; these were excised. The heart was freed, and the pericardial defect was closed by raising a flap of pleura posteriorly and suturing it to the edges of the pericardial defect. Histology of the resected nodules showed local recurrence of malignant thymoma. Her postoperative course was uncomplicated. Follow-up chest roentgenogram (Fig 3) and computed tomographic scan showed that her heart had returned to a central position. Forty-four months after her initial operation she is alive without evidence of metastases.

Comment

The effects of cardiac torsion are related to the nature of the cardiac malposition. For right sided herniations or torsions, superior vena cava syndrome of the upper half of the body develops [5], whereas for left-sided herniations, patients may present with hypotension [6] due to

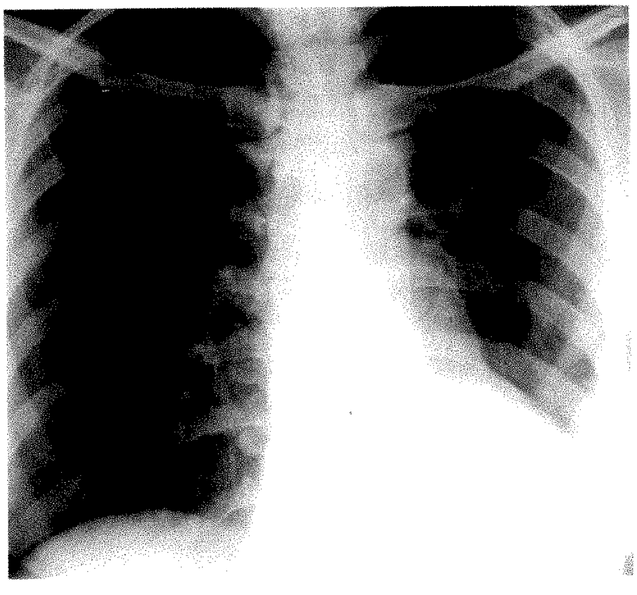

Fig 3. Posteroanterior chest roentgenogram after correction of cardiac torsion, with return of the normal left heart border.

strangulation of the ventricular walls by the edges of the pericardial sac. In the presented case of left-sided cardiac herniation, the heart had undergone organoaxial torsion, with displacement of the apex of the heart into the posterior costophrenic recess. Reduction of the heart to the midline at thoracotomy restored the ventricular function and equalized the previous difference in the pulsation volume of the carotid and femoral arteries.

Our patient had typical symptoms of increasing dyspnea and displacement of the apex beat posteriorly, together with abnormalities of the electrocardiogram [7] and chest roentgenogram [5]. However, this case was unusual for its late development of torsion and gradual onset of symptoms. In a review of 25 cases from the literature, Deiraniya [8] found that all cardiac herniations or torsions occurred within 24 hours of pneumonectomy. The scarcity of recorded cases of late torsion may be a result of the rapid development of adhesions between the heart and pericardium, which have been shown to occur within 3 days of operation. The rapid onset of herniation, with or without torsion, after intrapericardial pneumonectomy is a result of the large space vacated by the resected lung. Under these circumstances, cardiac herniation may be precipitated by the application of negative suction to the chest tube, coughing, or positive-pressure inflation of the remaining lung. At the time of operation it was thought unnecessary to close the pericardial defect because the lower left lobe had expanded well to fill the left hemithorax after left upper lobectomy. This may explain the more gradual development of herniation in our patient.

In unrecognized cardiac torsions, the mortality is 100%, but even after surgical intervention a 50% mortality has been recorded [8]. The clinician must remain vigilant in the follow-up of patients who have had partial lung resections, in whom surgically created pericardial defects have not been closed at the time of operation, if potentially fatal late-developing cardiac torsions are not to be missed.

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Inaccuracy of Cardiac Output by Thermodilution During Acute Tricuspid Regurgitation

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We have been comparing cardiac output measured with a novel Doppler pulmonary artery catheter to that measured by thermodilution and aortic electromagnetometry in cardiac surgical patients. We report here our observation of a nearly twofold increase in thermodilution cardiac output after the acute intraoperative onset of tricuspid regurgitation that was not confirmed by the novel catheter or direct measurement of aortic blood flow. We conclude that in some patients, acute tricuspid regurgitation may lessen the reliability of thermodilution cardiac output.

(Ann Thorac Surg 1992;53:706–8)

Although the accuracy of thermodilution (TD) determination of cardiac output in the presence of tricuspid regurgitation has been questioned [1–3], a variety of studies have provided conflicting results [4–6]. Alternatively, tricuspid regurgitation clearly alters TD determination of right ventricular ejection fraction [7].

Recently, a Doppler pulmonary artery catheter (DPAC) capable of directly measuring pulmonary arterial blood flow velocity and cross-sectional area, and calculating continuous cardiac output, was introduced. Animal studies have demonstrated an excellent correlation of DPAC-measured cardiac output with the common laboratory standard, electromagnetometry (EM) [8]. We have been comparing cardiac output measurements obtained by TD, DPAC, and EM in cardiac surgical patients under a protocol approved by our institutional human studies committee. We report here our observation of a marked change in TD cardiac output, unaccompanied by similar alteration in DPAC flow, after acute development of tricuspid regurgitation in a patient undergoing coronary arterial bypass grafting.

A 62-year-old, 100-kg, 198-cm male was scheduled to undergo coronary artery bypass grafting. Past medical history was remarkable for hypertension, nephrolithiasis, gout, and progressive exertional angina. There was no history of congestive heart failure or valvular dysfunction. Cardiac catheterization showed severe coronary artery disease involving the left main, left anterior descending, first diagonal, left circumflex, obtuse marginal, and right coronary arteries. Left ventricular function was normal; right heart angiography was not performed. Preoperative medications included nitroglycerin (Nitro-Bid; Marion Laboratories, Kansas City, MO), nifedipine (Procardia; Pfizer Laboratories, New York, NY), atenolol (Tenormin; ICI Pharma, Wilmington, DE), and allopurinol.

Before induction of anesthesia, a DPAC (Flocath; Cardiometrics, Inc, Mountain View, CA) was placed through the right internal jugular vein. This 7.5F catheter contains Doppler ultrasonic transducers 13 cm from the tip to directly measure pulmonary arterial blood flow velocity and cross-sectional area and to allow beat-to-beat determination of cardiac output. The catheter is also equipped with a thermistor to allow for conventional thermodilution measurement of blood flow. During the procedure, electrocardiogram, right radial arterial pressure, pulmonary arterial pressure, and central venous pressure were monitored and continuously recorded on a strip chart along with DPAC cardiac output.

Anesthesia was induced with fentanyl and lorazepam, and relaxation was attained with vecuronium. After uneventful tracheal intubation, a transesophageal echocardiographic probe was placed to evaluate valve function and regional wall motion. Heart rate and rhythm; radial arterial, pulmonary arterial, and central venous pressures; and averaged cardiac output measurements at specific time points are shown in Table 1. All TD measurements were obtained in triplicate at end-expiration using 10 mL of room-temperature injectate and were compared with DPAC and EM (when available) values displayed at the moment of injection.

After sternotomy, but with the pericardium intact, neither color-flow nor pulsed Doppler (Fig 1) transesophageal echocardiographic assessment of the tricuspid valve revealed tricuspid regurgitation, and cardiac output measured by TD and DPAC were similar. After pericardiotomy and construction of a pericardial sling, moderate tricuspid regurgitation was evident by pulsed-Doppler transesophageal echocardiography (Fig 2), and radial arterial, pulmonary arterial, and central venous pressures and DPAC flow were virtually unchanged while TD cardiac output had almost doubled. Placement of the EM flow probe on the ascending aorta (Model 701 D; Carolina

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Table 1. Hemodynamic Variables During Coronary Artery Bypass Grafting

Time Point	HR (beats/min) [rhythm]	AP (mm Hg)	PAP (mm Hg)	CVP (mm Hg)	TD CO (L/min)	DPAC CO (L/min)	EM CO (L/min)	TR
Before induction	54 [NSR]	138/62	22/12	4	8.1	7.8	NA	None
After induction, chest closed	50 [NSR]	130/60	24/13	3	5.1	6.3	NA	None
After sternotomy, pericardium intact	52 [NSR]	140/64	21/7	3	4.3	4.6	NA	None
After pericardiotomy	58 [NSR]	124/65	23/10	5	7.1	4.4	4.1	Moderate
Cannulated for CPB	66 [AF]	116/56	21/9	5	3.6	3.1	3.4	Moderate
Decannulated after CPB	90 [VP]	128/60	21/10	6	6.5	7.9	8.5	Mild
Chest closed	90 [VP]	122/78	20/14	7	5.3	5.7	NA	Trace

AF = atrial fibrillation; AP = radial arterial pressure; CPB = cardiopulmonary bypass; CVP = central venous pressure; DPAC CO = cardiac output measured by Doppler pulmonary artery catheter; EM CO = cardiac output measured by aortic electromagnetometry; HR = heart rate; NA = not available; NSR = normal sinus rhythm; PAP = pulmonary arterial pressure; TD CO = cardiac output measured by thermodilution; TR = tricuspid regurgitation; VP = ventricular pacing.

Medical Electronics, Inc, King, NC) measured an aortic blood flow similar to DPAC flow. Atrial fibrillation subsequently developed during cannulation for cardiopulmonary bypass; under these conditions cardiac output measured by all three techniques was similar.

Coronary revascularization and weaning from cardiopulmonary bypass were uneventful. Shortly after weaning there was resumption of atrial fibrillation, which did not respond to cardioversion; ventricular pacing was instituted to augment a native rate of slightly more than 60 beats/min, and procainamide infusion was begun. Transesophageal echocardiography continued to demonstrate moderate tricuspid regurgitation. Cardiac output measured by all three methods showed a cardiac index of more than 2 L/min; however, TD flow measurements were 25% less than EM measurements, which were similar to those obtained by DPAC. After chest closure, only trace tricuspid regurgitation was evident by transesophageal echocardiography, and TD and DPAC cardiac outputs were similar.

Comment

It has long been speculated that tricuspid regurgitation alters TD determination of cardiac output, with theoretical considerations having been described for both underestimation and overestimation [3–5]. Clinical studies have provided conflicting data [5, 6], and a study of experimentally induced tricuspid regurgitation in dogs failed to demonstrate significant error, although only 4 animals were assessed [4].

In the patient presented here, removing pericardial restraint apparently changed right ventricular compliance, allowing sufficient dilatation to produce acute tricuspid regurgitation. Subsequently, a large increase in TD cardiac output was measured that could not be confirmed by either DPAC or EM. Thermodilution measurement of cardiac output utilizes a modification of the Stewart-Hamilton equation, which considers injectate volume along with specific gravity, specific heat, and temperature of both injectate and blood, as well as a correction factor for warming of injectate along the catheter. The denominator of the equation also includes the area under the curve for dilution of cold injectate back to baseline temperature, and thus blood flow is inversely proportional to area under the curve. In that other factors in the equation essentially remain constant, the major variable in TD determination of cardiac output is area under the curve. Both experimental and clinical studies have demonstrated

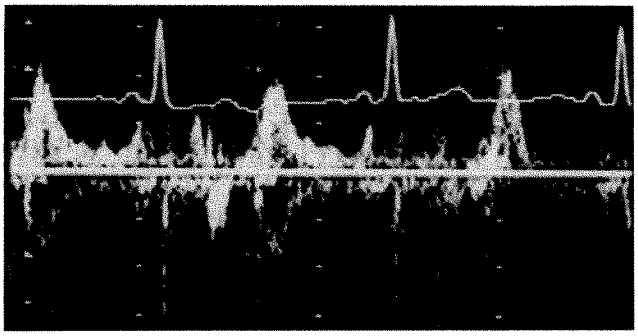

Fig 1. Electrocardiogram (lead II) and pulsed Doppler measurement of transtricuspid blood flow velocity before pericardiotomy.

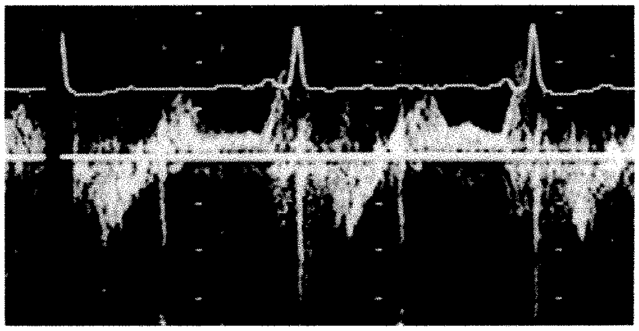

Fig 2. Electrocardiogram (lead II) and pulsed Doppler measurement of transtricuspid blood flow velocity after pericardiotomy. Velocity wave below central reference line after QRS complex on electrocardiogram represents tricuspid regurgitation during mechanical ventricular systole.

alterations in morphology of the thermodilution curve during tricuspid regurgitation [1, 4]. Theoretically, recirculation of cold injectate will prolong the thermodilution curve, increasing total area under the curve and underestimating cardiac output. Alternatively, if regurgitated injectate loses indicator to (cools) surrounding tissue (ie, atria, venae cavae), the thermodilution curve may be curtailed, decreasing area under the curve and overestimating cardiac output. Thus, the effect of tricuspid regurgitation on TD determination of cardiac output is probably influenced by multiple factors such as rate of venous return and pulmonary vascular resistance (altered regurgitant fraction).

The mechanism behind the response in the patient presented here is unclear but may reflect abnormal mixing of blood and cold injectate with premature temperature loss secondary to bidirectional flow across the tricuspid valve. Although central venous pressure was not altered by the onset of tricuspid regurgitation, in the setting of increased right heart compliance venous return may have increased, thus contributing to rapid dilution of regurgitated injectate. It is interesting that the disparity in TD and DPAC flow resolved after the onset of atrial fibrillation, perhaps due to an attendant change in right atrial filling dynamics. It is also important to note that after cardiopulmonary bypass, again in the setting of atrial fibrillation, TD appeared to underestimate cardiac output (in comparison with both DPAC and EM), and that along with the tricuspid regurgitation, the disparity between TD and DPAC resolved after closure of the chest.

In that the directional error in TD cardiac output reported here was inconsistent (ie, overestimation followed by underestimation), this case report would appear to reflect the controversy regarding the effect of tricuspid regurgitation on the accuracy of cardiac output measurement by TD. As evidence accumulates to indicate an increasing incidence of tricuspid regurgitation with age [9], it is important for clinicians to appreciate potential limitations of TD and interpret the value in the context of other clinical indices. Furthermore, novel methods to assess cardiac output that are unaffected by valve function and can be clinically applied deserve further study.

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Saphenous Bicephalic Aortocoronary Graft in the Treatment of Right Coronary Bifurcation Stenosis

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We describe a surgical maneuver suitable for stenosis of the bifurcation of the right coronary artery. The distal end of a saphenous vein graft is prepared to obtain a two-headed shape. The anastomosis achieves enlargement of the bifurcation, providing complete distal revascularization.

(Ann Thorac Surg 1992;53:709–10)

Severe, stenotic or occluding atherosclerosis is sometimes located at the bifurcation of the right coronary artery. If the patient needs surgical revascularization, the treatment may be challenging in case of diffuse narrowing with extension to the posterior descending artery (PD) and to the left lateral branch (LLB). The surgeon then has the option of several solutions: the simplest is a single bypass graft to one of the two distal branches, usually the PD, which is easier to access, but revascularization remains incomplete and may lead to residual ischemia if both peripheral arteries are important. To avoid this, there are more time-consuming solutions, such as separate bypass grafts to PD and LLB, or more technically demanding solutions, such as sequential grafting or endarterectomy, the latter being moreover uncertain regarding postoperative cardiac morbidity [1]. The surgical maneuver described here achieves complete distal revascularization using a single previously tailored venous bypass graft.

Technique

Arteriotomy usually starts 1 cm proximal to the bifurcation. After the lumen is entered, the incision is extended through the stenosis, toward the PD beyond the pathologic zone. From inside the lumen, the LLB ostium is identified, and a perpendicular incision started right above it is continued to healthy wall (Fig 1). In case of total occlusion, arteriotomy is first made on the PD, then extended proximally.

A saphenous vein not less than 4 mm in diameter is then cut obliquely, just enough to adjust the length to the length of the arteriotomy directed to the PD. Then the toe of the graft is incised more or less medially, depending on the direction and the caliber of the LLB, and more or less deeply according to the length of the LLB arteriotomy (Figs 2, 3). Anastomosis is performed using a continuous 7-0 polypropylene suture (Fig 4).

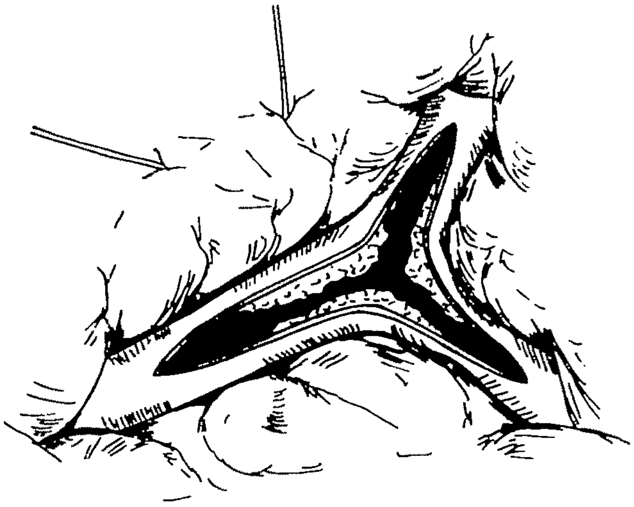

Fig 1. Right coronary artery bifurcation. Arteriotomy is prolonged through the stenosis to healthy wall of the posterior descending artery and the left lateral branch.

Since August 1989, this technique has been used in 23 patients out of a group of 380 operated on for coronary artery bypass grafting during a 14-month period. Postoperative exercise tests were negative in all patients; 1 patient operated on at the early phase of infarction had control catheterization showing patency of the graft with excellent run-off (Figs 5, 6).

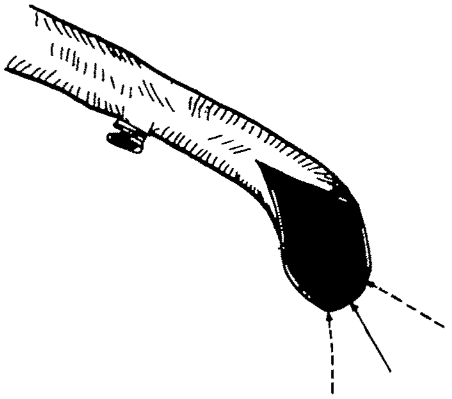

Fig 2. Preparation of bicephalic saphenous vein. The site of toe incision depends on the direction and the width of the left lateral branch.

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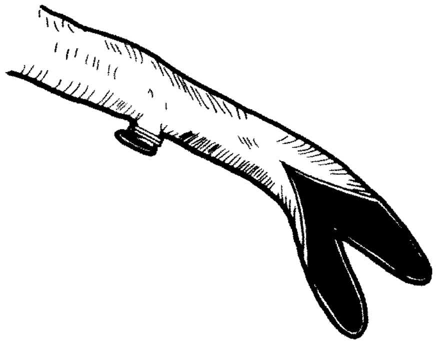

Fig 3. Preparation of bicephalic saphenous vein. The length of the incision is adjusted to the arteriotomies.

Comment

This particular lesion is not rare, and its treatment may be difficult and time consuming if the surgeon searches for complete revascularization. By the same token, planning what to do is not always possible because the severity and the exact extension of the lesion are sometimes recognized intraoperatively, once the artery is open. In those cases, where adaptation to the findings is required, this technique is useful.

New uses of saphenous vein may appear obsolete, now that the surgical trend concerning coronary revascularization is arterialization. We agree and note that, during the same period, 97% of our patients had at least one arterial graft (left or right internal thoracic artery or both, right gastroepiploic artery or epigastric artery). However, many patients with multiple-vessel involvement need venous grafts because the number of bypass grafts required is high or because the lesions are complex or too far for in situ or even free arterial grafts.

The proximal part of the anastomosis includes the pathological arterial wall. This may lead to difficulties in constructing the suture line, particularly in the presence of dense calcifications. Nevertheless, even in those cases we never had to proceed with an endarterectomy as the stitches could be placed close to the edge of the arteriotomy.

We have no long-term angiographic controls, but no patient experienced recurrence of the angina up to 14 months postoperatively, which suggests a long-term patency similar to that of a standard vein graft.

Facing a tedious, sometimes unexpected, and not rare coronary atherosclerotic lesion, this technique safely achieves complete revascularization, saving time and venous graft length.

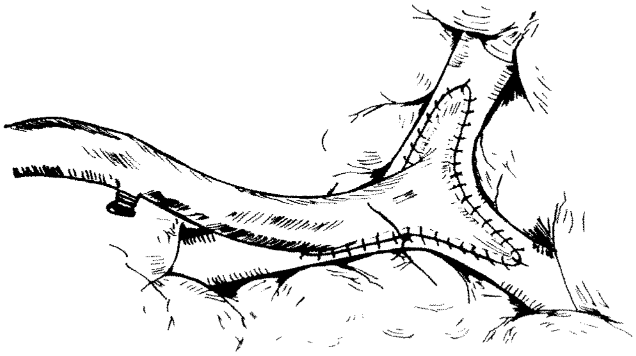

Fig 4. Anastomosis with a continuous 7-0 polypropylene suture.

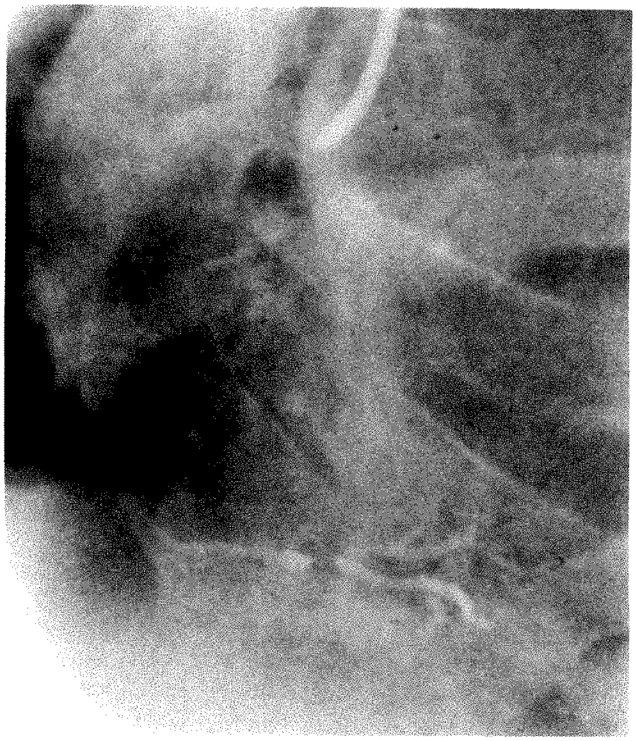

Fig 5. Subtotal stenosis responsible for inferior acute infarction operated on at the early phase.

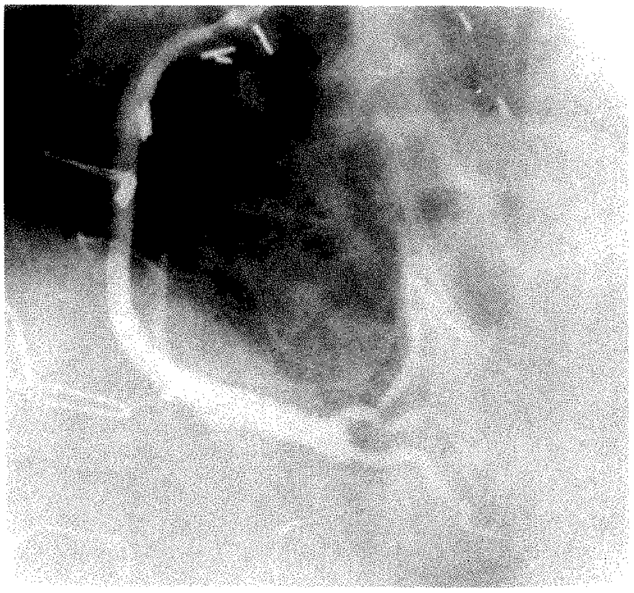

Fig 6. Control catheterization showing patent anastomosis and excellent run-off.

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Percutaneous Replacement Jejunostomy

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After esophagectomy in which a surgical jejunostomy is performed, there is a small group of patients whose jejunostomy tube has been removed who require late postoperative nutritional support. For these patients, a percutaneous replacement jejunostomy technique is described that is simple and safe and that allows for enteral alimentation.

(Ann Thorac Surg 1992;53:711–3)

The importance of maximizing a patient's nutritional status in preparation for and during recovery from an esophageal operation is widely accepted. It is our routine to perform a surgical jejunostomy in all patients undergoing esophageal resection. In uncomplicated cases, the jejunostomy tubes are removed before discharge. There is a small group of patients who are initially well who require late postoperative nutritional support. For these patients, a technique is described for percutaneous replacement of the jejunostomy tube.

Technique

At operation, the intubated loop of jejunum must be prepared to permit later percutaneous intubation. We use a 14F red rubber catheter for our initial jejunostomy tube, which is passed through the anterior abdominal wall and into the proximal jejunum through a 2-0 chromic pursestring. A short Witzel tunnel is created. The intubated jejunum loop is tacked to the abdominal wall in a Stamm fashion using four 4-0 silk stitches. Each tacking stitch is marked with a metal hemostatic clip (Hemoclip; Edward Weck and Co, Research Triangle Park, NC) creating a square or rectangular "target." The jejunal loop is oriented with the proximal end cephalad and the distal end caudad. In addition, more recently we have marked the distal jejunum with several metallic clips (Fig 1). After the jejunostomy tube is removed and the tract allowed to heal, the tube may be replaced percutaneously in the catheterization laboratory.

Using local anesthesia with intravenous sedation, percutaneous entry into the jejunum is accomplished with a standard angiographic needle under fluoroscopic guidance by directing the initial puncture site at the surgically placed metal clip "target." After entry into the jejunum, air is instilled into the bowel to determine the direction of the distal jejunum. Injection of contrast medium also confirms an intraluminal needle placement (Fig 2). A 0.035-inch Wholey Hi-Torque modified J guidewire (Peripheral Systems Group, Mountain View, CA) is placed through the needle and directed distally into the jejunum. A 5.2F, 65-cm-long C-1 Cobra catheter (Cordis, Miami, FL) is used to direct the guidewire through the more proximal jejunal loops. To advance the guidewire even farther, the Cobra catheter is exchanged for a 7F, 125-cm-long MPA-2 multipurpose catheter (Cordis) with a 0.038-

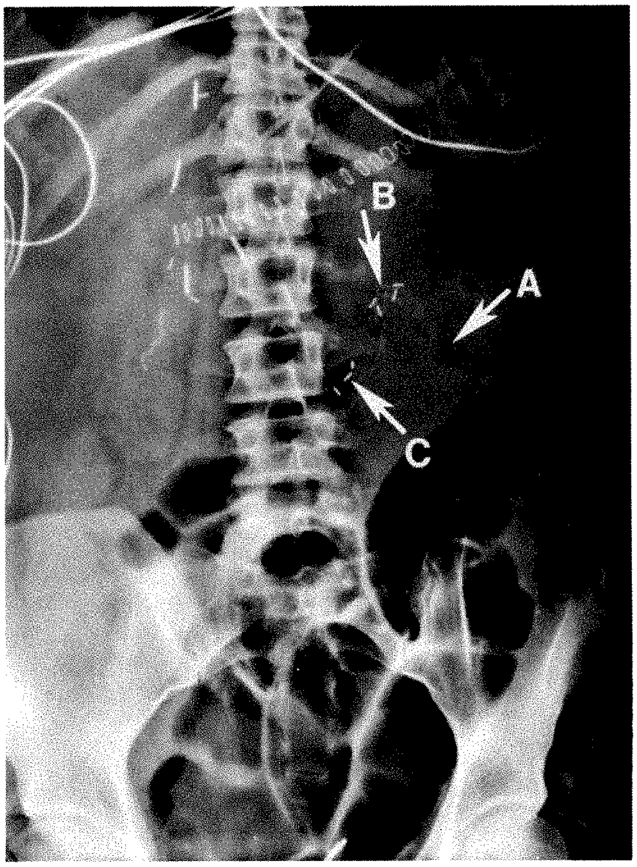

Fig 1. The radiographic appearance of a surgical jejunostomy prepared for later percutaneous access: (A) indicates the jejunostomy tube, (B) the metal clip "target," and (C) metal clips that mark the direction of the distal jejunum.

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inch inner diameter. This 7F multipurpose catheter is advanced into the small bowel, and the Wholey wire is exchanged for a 0.038-inch, 260-cm-long Amplatz extrastiff guidewire. The percutaneous tract is then sequentially dilated using 8F, 12F, and 14F dilators. The last dilator is 16F with an accompanying peel-away sheath (Cook, Bloomington, IN). Through this introducer, a 16.5F, 80-cm-long double-lumen Carey-Alzate-Coons gastrojejunostomy tube (Cook) is placed. The tube's position is confirmed on fluoroscopy (Fig 3), and the gastrojejunostomy tube is secured in place with a self-retaining Malecot retention lock (a part of the gastrojejunostomy tube) (Fig 4). The catheter is left open to straight drainage for 24 hours and may then be used for enteral feedings.

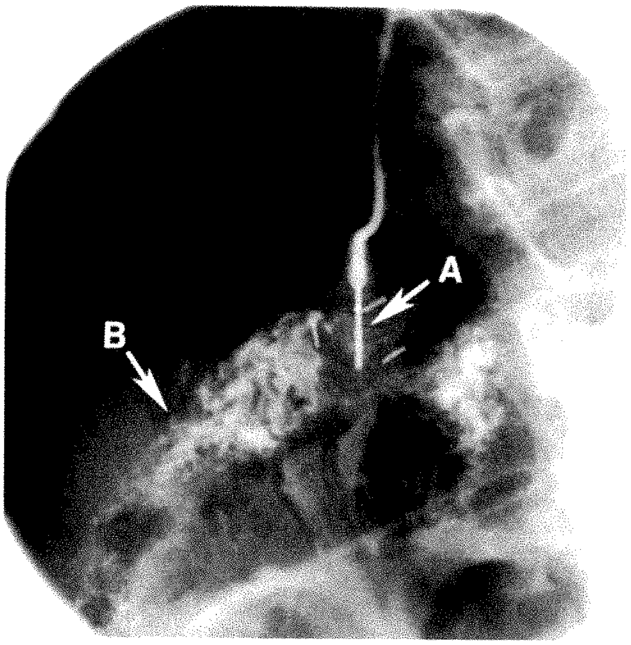

Fig 2. Using fluoroscopic guidance, the previously intubated jejunal loop is entered percutaneously through the metal clip "target" using a standard angiographic needle (A), and contrast medium is injected to confirm an intraluminal puncture (B).

Comment

The importance of nutritional support in the management of patients undergoing esophageal resection is widely accepted. The advantages of enteral feedings over total intravenous nutritional support include maintenance of the gastrointestinal mucosal barrier, lower cost, easier home care, and the fact that it does not require central intravenous access, which may be limited from preoperative adjunctive therapy, or perioperative care.

It is our practice to perform a surgical jejunostomy in all patients undergoing esophagectomy. In uncomplicated cases, the jejunostomy tube is removed before discharge. The tube is left in place if there is any question about the patient's medical or nutritional status. There is a small group of patients whose jejunostomy tube has been removed who require late postoperative nutritional support. In our experience, this is uncommon, occurring in 3 of 84 patients (3.6%) undergoing esophagectomy for carcinoma. Rather than leave all jejunostomy tubes in over the long term prophylactically, we developed the percutaneous replacement jejunostomy technique, which has worked successfully in 2 patients (the first of 3 patients was treated before this technique was devised).

Others have described techniques for nonoperative jejunostomy replacement. Westfall and co-workers [1] reported a direct percutaneous endoscopic jejunostomy technique, which they used successfully in 2 postesophagogastrectomy patients with recurrent carcinoma. Their technique requires a previous operative jejunostomy and close approximation of the jejunal loop to the anterior abdominal wall. Gray and associates [2] reported a technique for direct percutaneous jejunostomy in a single patient in which a free air-filled loop of jejunum adjacent to the abdominal wall was directly punctured. Others have reported a similar technique in which the stomach was percutaneously intubated and a catheter threaded fluoroscopically into the jejunum [3-5].

The percutaneous replacement jejunostomy technique that we describe is simple and safe. The technique may also be repeated without additional patient preparation. For patients undergoing esophagectomy, it is now our routine approach to prepare the operative jejunostomy site for later percutaneous access.

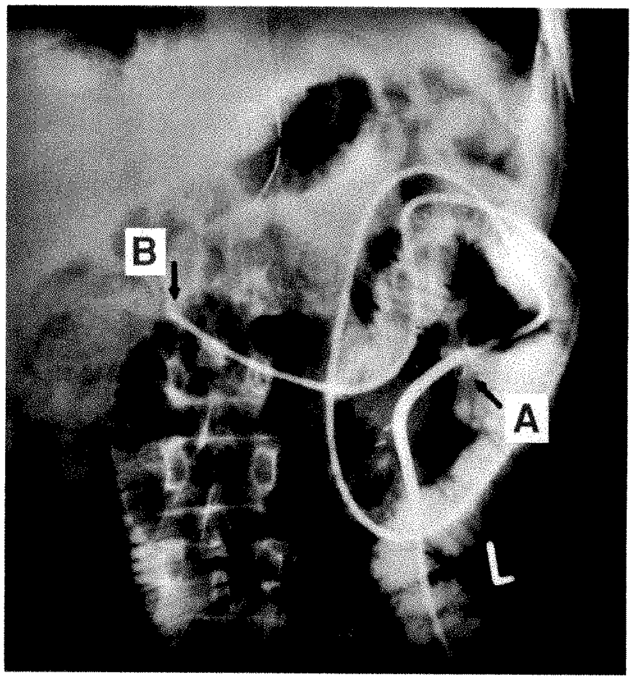

Fig 3. After the percutaneous tract (A) is sequentially dilated, a gastrostomy tube is threaded distally (B) into the jejunum.

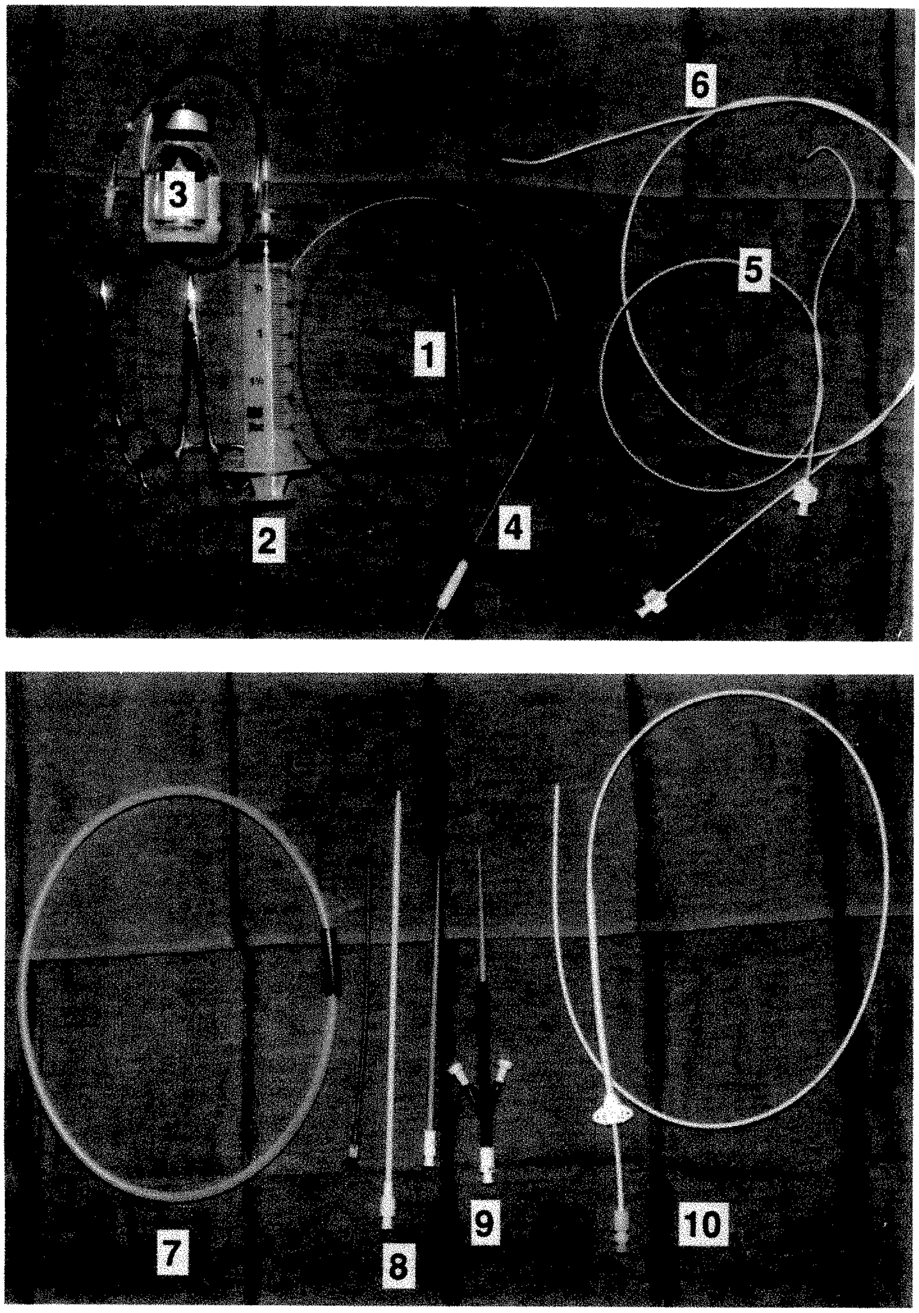

Fig 4. The supplies necessary to percutaneously replace the jejunostomy tube are sequentially displayed: (1) hollow-bore needle, (2) syringe with intravenous extension tube for air injection, (3) radiographic contrast medium to confirm intraluminal needle position, (4) Wholey Hi-Torque wire, (5) C-1 Cobra catheter, (6) MPA-2 multipurpose catheter, (7) Amplatz extra-stiff guidewire, (8) 8F, 12F, and 14F dilators, (9) 16F peel-away sheath, and (10) Carey-Alzate-Coons gastrojejunostomy tube (see text).

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Retrograde Cardioplegia: Detail for Coronary Sinus Cannulation Technique

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Minneapolis Heart Institute, Minneapolis, Minnesota

This communication stepwise describes transatrial cannulation of the coronary sinus, a technique that we found to be very simple, fast, reproducible, and free of complication.

(Ann Thorac Surg 1992;53:714–5)

In spite of descriptive detail of the technique provided by Buckberg [1] and by Gundry and associates [2], the use of transatrial cannulation of the coronary sinus for delivery of cardioplegia has not been widely accepted due to various technical difficulties.

Since November 1989, the technique previously described has been gradually more defined and used in more than 700 patients. This communication will stepwise describe atrial cannulation of the coronary sinus, a technique that we found to be very simple, fast, reproducible and free of complication. *However, this technique works only with the flexible-stylet retrograde cannula. The other commercially available retrograde catheter is not amenable to this particular approach due to the preformed stylet.* The technique has been used in all open heart cases including coronary artery bypass, valve, and aortic operations.

Technical Detail

Cannulation for cardiopulmonary bypass is carried out in the usual fashion with a single-stage venous cannulation technique. Cardiopulmonary bypass is initiated to avoid hemodynamic and rhythm instability. As soon as cardiopulmonary bypass is established, while the heart is still beating and before a left ventricular vent is inserted (if used), a pursestring suture is applied about 1 cm distal to the venous cannulation site at the right atrial appendage (Fig 1). At this point, the assistant's right hand is pulling on the venous cannula and the right atrium toward the patient's left shoulder (indicated by the *arrow* in the illustration). At the same time, the perfusionist restricts venous return, keeping the right atrium moderately distended. While the *heart is still beating* and ejecting, a small stab wound is made inside the previously placed pursestring. The retrograde coronary sinus catheter with *straight* stylet in place is held with the surgeon's left hand. The catheter is then inserted into the right atrium and placed *anterior* to the venous cannula. The surgeon's right hand is placed along the diaphragmatic surface of the heart. The index or long finger, placed at the inferior vena cava and atrioventricular groove junction, is used to locate the catheter tip and gently guide it into the coronary sinus and greater cardiac vein. The stylet is removed, and the flexible catheter is advanced forward. Placement of the tip of the catheter 1 to 2 cm proximal to the left atrial appendage allows liberal infusion without wedging of the tip.

Confirmation of the placement is obtained by manually palpating the catheter or the inflated balloon in the atrioventricular groove. If not felt, it is certain that the catheter is not in place and most likely is in either the right ventricle or inferior vena cava. The catheter is secured by

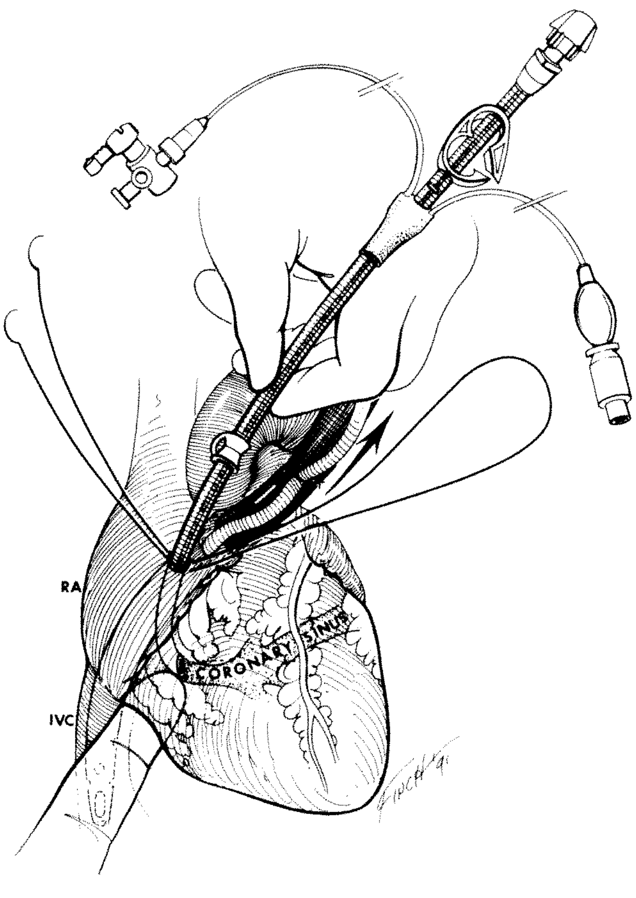

Fig 1. Coronary sinus catheter with straight stylet in place being inserted into the right atrium (RA) anterior to the venous cannula. The right atrial appendage is pulled toward the patient's left shoulder (arrow), thus directing the coronary sinus ostium cephalad in line with the atrial cannulation site. (IVC = inferior vena cava.)

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snaring the catheter and ligating with a free tie around the movable ring on the cannula, after checking to assure there is no excessive catheter loop in the right atrium. The catheter is connected to the pressure and the cardioplegic lines.

Comment

The technique prescribed herein eliminates the cannulation from the left side of the table, which is inconvenient and cumbersome. A few points, however, need to be emphasized to make the technique successful and reproducible: (1) Insert the catheter high in the right atrium, close to the right atrial appendage. (2) Do not bend the catheter. (3) Pull the venous cannula and the right atrium toward the patient's left shoulder, thus directing the coronary sinus ostium cephalad, in line with the right atrial cannulation site.

Always palpate the catheter in the atrioventricular groove before each cardioplegic infusion. If it is not palpable, then it is certain the catheter is not in the correct location. Coronary sinus pressure may be increased during the infusion, particularly during the elevation of the heart, from the catheter wedging. Gentle retraction of the catheter without untying the securing suture will eliminate this problem.

Cannulation of the coronary sinus was successful in 99% of the cases, but there were occasional cases when advancement of the catheter into the greater cardiac vein was not possible due to anatomical variations. In these particular situations, the balloon is moderately inflated and cardioplegic infusion is begun while the surgeon's right index or long finger is pressed distal to the balloon to prevent dislodgement. Repositioning of the catheter may, however, become necessary during the procedure.

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The acquisition of new knowledge in thoracic surgery is a continuum. Ideas and practices may change significantly as a result of experience, but there have been limited ways to communicate easily the reasons for such modifications.

The purpose of this section is to present brief follow-up reports from authors whose work was previously published in The Annals of Thoracic Surgery. *The goal is to learn whether the original conclusions have stood the test of time, and whether or not previously recommended techniques have been modified, replaced, or discarded. Contributions to* Update *are short progress reports that do not preclude subsequent more complete articles.*

Thomas B. Ferguson, MD, Editor
John R. Benfield, MD, Associate Editor

1990: Results of Internal Thoracic Artery Grafting Over 15 Years: Single Versus Double Grafts

Andrew C. Fiore, MD, Keith S. Naunheim, MD, Phillip Dean, MD,
George C. Kaiser, MD, D. Glenn Pennington, MD, Vallee L. Willman, MD,
Lawrence R. McBride, MD, and Hendrick B. Barner, MD

Divisions of Cardiothoracic Surgery, St. Mary's Health Center and St. Louis University Medical Center, St. Louis, Missouri

One hundred consecutive patients who had coronary artery bypass grafting using both internal thoracic arteries (ITAs) and saphenous veins, operated on during a 3-year period between 1972 and 1975, have been compared retrospectively with a series of 100 patients operated on during the same period who had one ITA graft along with saphenous vein grafts. The two groups were similar with respect to age, sex, risk factors for coronary artery disease, angina class, extent of coronary artery disease, left ventricular function, number of coronary bypass grafts performed, and completeness of revascularization. Single ITA operative mortality was 2% and double ITA, 9% (p = NS). The mean follow-up of hospital survivors was 14.4 ± 2.7 years; all but 7 patients had follow-up for at least 10 years. At 13 years, the actuarial patency of the right ITA was 85% and the left ITA, 82%. These data strongly suggest a survival benefit for patients with double ITA grafts among hospital survivors (74% versus 59%; $p = 0.05$). Patients receiving two ITA grafts had a significant freedom from subsequent myocardial infarction (75% versus 59%, $p < 0.025$), recurrent angina pectoris (36% versus 27%, $p < 0.025$), and subsequent total ischemic events (32% versus 18%, $p < 0.01$). These data also suggest improved freedom from coronary artery interventional therapy (percutaneous transluminal coronary angioplasty and reoperation) when two ITA grafts were used. These results support the use of bilateral internal thoracic artery grafting in selected patients.

(Ann Thorac Surg 1990;49:202–9)

1992 Update: Keith S. Naunheim, MD, Hendrick B. Barner, MD, and Andrew C. Fiore, MD

Department of Surgery, St. Louis University Medical Center, St. Louis, Missouri

Since publication of our recent article [1] reporting the long-term results of the use of double internal thoracic artery (ITA) grafts in the coronary artery bypass operation, we became concerned over our inability to secure a more complete follow-up of this important group of patients. Therefore, we have made a more vigorous effort to trace the previously untraced patients, and have finally secured a more complete follow-up with the help of Drs E. H. Blackstone, John W. Kirklin, and their colleagues.

Twenty patients in our original study could not be contacted after 1987, and most of these were untraced since the early 1980s. With this renewed effort, 13 of these 20 were traced. Of these, 9 had received double ITAs and 5 were dead, whereas 4 had received single ITAs and 1 was dead. Because of the possibility that this new information might change the inferences from the study, we asked Drs Blackstone and Kirklin to redo the survival analysis. This analysis (Fig 1) showed a slight advantage in regard to survival for single ITA (versus double ITA) in the early period after operation. This was due to the higher operative mortality in our double ITA patients during the early 1970s. There was, however, a slight survival advantage of double ITA over single ITA in the late period, although this difference could be due to chance alone (overlapping 70% confidence intervals). The hazard function for each group has confidence intervals that are just touching at about 15 years after operation, indicating that the instantaneous risk of death late postoperatively in the groups as a whole may be higher when the single ITA is used (Fig 2). The prevalence of risk factors in the two groups was somewhat different, and therefore an additional analysis was made. For this, the two groups were put into a single group (Fig 3). By univariate analysis of the single group, use of the double ITA was probably ($p = 0.07$) a risk factor for death in the

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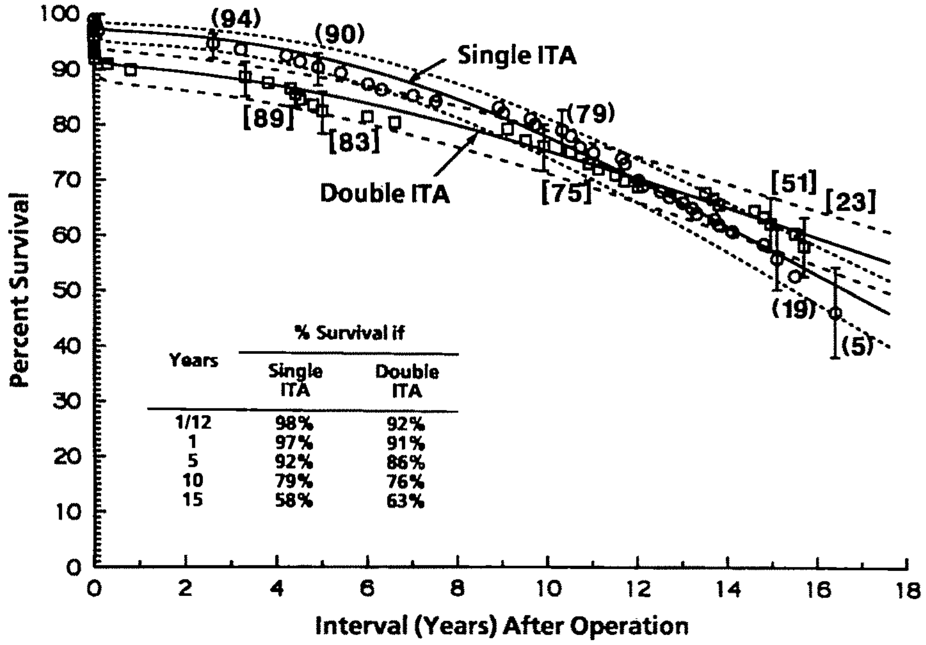
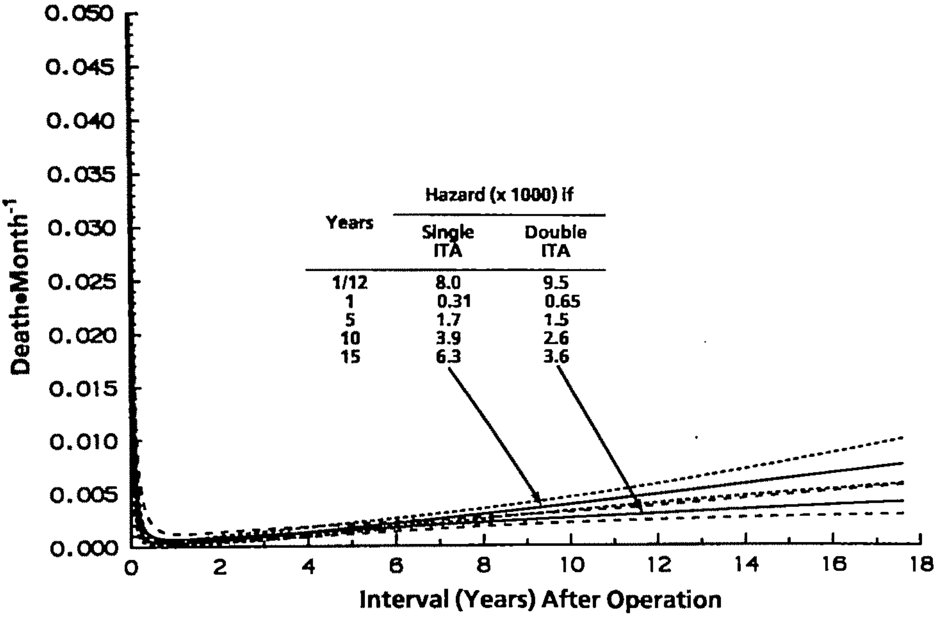


Years	% Survival if Single ITA	% Survival if Double ITA
1/12	98%	92%
1	97%	91%
5	92%	86%
10	79%	76%
15	58%	63%

Fig 1. Survival analysis including additional follow-up. (ITA = internal thoracic artery.)

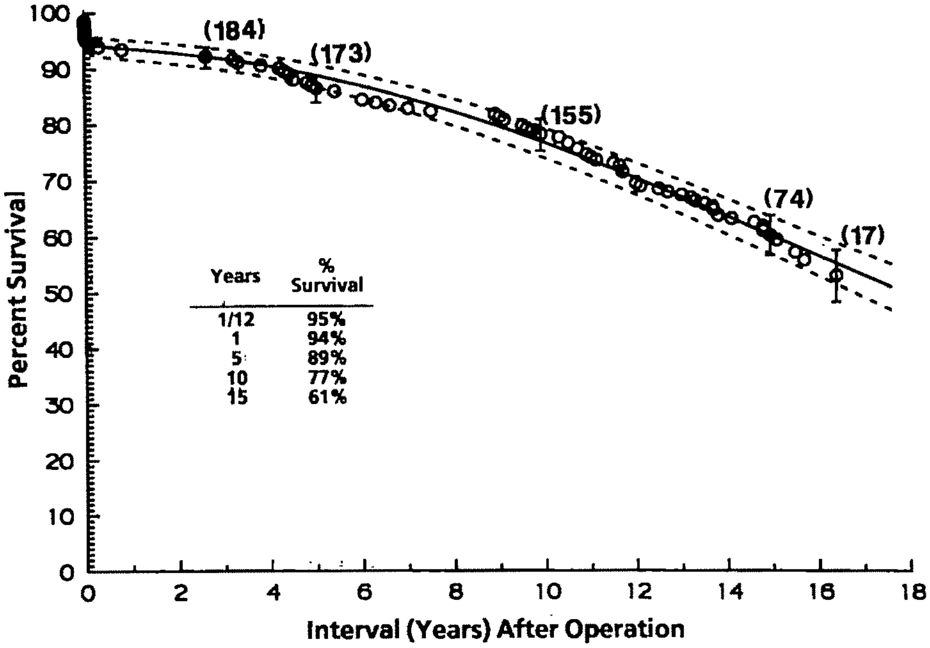
early period after operation (single ITA probably had an advantage); single ITA was only possibly ($p = 0.15$) a risk factor for death in the late postoperative period (double ITA only possibly had an advantage). However, the multivariate analysis made it evident that once even preliminary steps were taken to adjust outcome according to risk factors, the increased risk of double ITA grafting early after operation became more certain ($p < 0.03$) and the late benefit of double ITA grafting lost any suggestion of significance ($p = 0.60$).

Our early experience with double ITA grafting yielded a 9% operative mortality. Since that time, our overall operative mortality for double ITA grafting has been reduced to 2.2% (1985 to 1990). This is nearly identical to the mortality rate of single ITA grafting, and therefore, in our recent report, we analyzed only hospital survivors. Although this was not a statistically "pure" method of handling the two groups, it was not a randomized series and the intent of our article was to determine whether or not the long-term benefits of two ITA grafts were superior to those of revascularization with a single ITA graft. Because double and single ITA grafting can now be accomplished with similar operative mortalities, we decided in the original article to use only hospital survivors, hoping to remove any confusing effects from the greater operative mortality for double ITA grafting early in our experience. This analysis of hospital survivors suggested ($p = 0.05$) a benefit in 15-year survival for double ITA



Years	Hazard (x 1000) if Single ITA	Hazard (x 1000) if Double ITA
1/12	8.0	9.5
1	0.31	0.65
5	1.7	1.5
10	3.9	2.6
15	6.3	3.6

Fig 2. Hazard functions including additional follow-up. (ITA = internal thoracic artery.)



Years	% Survival
1/12	95%
1	94%
5	89%
10	77%
15	61%

Fig 3. Survival analysis with both groups combined.

grafting. Drs Kirklin and Blackstone kindly ran the same analysis as noted above for hospital survivors only. Even when only hospital survivors were included, the univariate analysis revealed that single ITA grafting in the late phase was only possibly a risk factor for death ($p = 0.16$). This suggests that double ITA grafting was not protective over the 15-year period with regard to survival. It should be noted that we did find significant improvements in the double ITA group with regard to freedom from angina, freedom from infarction, and freedom from all ischemic events.

In summary, although there does appear to be significant clinical benefit from the use of double ITA grafts, we cannot demonstrate any survival benefit in our patient analysis of long-term follow-up.

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Thoracic Surgery and the War Against Smoking: Richard H. Overholt, MD

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Richard H. Overholt was born at the beginning of the twentieth century when thoracic surgery hardly existed. During the first 20 years of his life progress in the field was slow. The next 20 years, which coincided with Overholt's surgical training and his early years as a thoracic surgeon, saw a rapid and almost explosive growth. Overholt's contributions were legion. They included the world's first successful right pneumonectomy, advancements in surgical treatment of tuberculosis, development of segmental resection, and introduction of the prone operative position. He was a bold and creative pioneer thoracic surgeon with consumate technical skills. Sixty years ago, when Overholt started his career as a thoracic surgeon, the hazards of smoking were not appreciated, the habit was fashionable, and consumption of tobacco was rapidly rising. In the early 1930s Overholt was among the very few physicians who recognized the perils of smoking and initiated a long but initially unrewarding antismoking crusade. By the early 1950s evidence about the ill effects of tobacco use began to accumulate. Organized medicine, voluntary health groups, and governmental agencies joined in a concerted effort to educate and to contain smoking. During the ensuing 30 years the antismoking movement achieved ever-increasing success. Today, it is widely recognized that smoking is a major health hazard and tobacco consumption is on the decline. Richard Overholt issued the first warning signals about the perils of tobacco and served as an indefatigable leader of the antismoking crusade throughout his professional career.

(Ann Thorac Surg 1992;53:719–25)

In the second year of this century, when Richard Overholt was born, thoracic surgery had barely been conceived. Tuberculous and suppurative diseases of the lung were rampant, debilitating, and frequently lethal. Bronchogenic carcinoma was less common. Roentgenography of the chest was in a developmental stage. Diagnosis of intrathoracic pathology was based almost exclusively on history and physical examination. Treatment was nonspecific and woefully inadequate. Clinical use of antibiotics and antituberculous drugs was almost half of a century away. Although anesthesia was discovered 50 years earlier, the potential of the endotracheal tube for delivering inhalational anesthesia or supporting respiratory mechanics during intrathoracic operations had not been recognized. The fundamentals of respiratory physiology were poorly understood so that rational treatment of mechanical respiratory derangements was not possible. The techniques and benefits of intercostal tube drainage were not appreciated. Entry into the pleural space was feared because, without the availability of protective measures, an open pneumothorax was associated with an almost certain lethal outcome. Although it was thought that excision of irreversibly damaged or pus-laden pulmonary tissue could save the life of the host, a safe operation to accomplish the task was not available. A few bold pioneering surgeons attempted pulmonary resections from time to time, but more patients died from the procedure than were helped by it. The first recorded pulmonary resection was performed in 1891 by the French surgeon, Tuffier [1]. He removed the tuberculous apex along a nonanatomic plane and through an extrapleural approach to avoid the dreaded open pneumothorax. Artificial pneumothorax, to collapse tuberculous cavities, was the only interventional therapy used with any semblance of regularity. However, the procedure was not always effective because in many cases pleural adhesions prevented collapse of the lung. In addition, after a few weeks the air was resorbed by the pleural surfaces and the lung reexpanded. Frequent refills, necessary to maintain the collapse, eventually resulted in tuberculous empyema. At the beginning of the twentieth century physicians realized that induced pneumothorax was not the panacea they had hoped for and looked for means to achieve permanent collapse. Sauerbruch in Germany proposed thoracoplasty as a way to achieve the goal [1].

Richard Overholt was born in 1901 in Ashland, Nebraska, and grew up in neighboring Peru, a hamlet with 300 residents set in the green, rolling countryside of the eastern part of the state. He went to school, from kindergarten through teachers college, in his small hometown. Both his parents were teachers. His mother and father were loving and strict churchgoing Methodists. They instilled in the Overholt children a strongly felt and faithfully practiced philosophy that God helps those who help themselves.

After graduation from teacher's college, Overholt

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moved to Panama, Nebraska, to start his first job as principal of the elementary school. He taught biology, chemistry, and physics and also coached the basketball team. He boarded with the local physician and the association left a lasting impact on his life. His host's library doubled as Overholt's bedroom. The rookie teacher discovered *Gray's Anatomy* on one of the shelves and was fascinated by what he saw about the intricacies of the human body. The book became his favored reading material and leisure-time companion. His interest in medicine was intensified by the house calls he made on patients at the invitation of his host. After each visit, he categorized the patient's illness in terms of his limited knowledge of anatomy and medicine and then turned to the library to look for the missing pieces. The seeds for working as a body mechanic, as Overholt referred to surgery, were planted. Within a year he enrolled at the University of Nebraska Medical School.

Another experience that played a major role in Overholt's career choice took place during his freshman year in medical school. While rounding a street corner on his bicycle Overholt was hit by a Model T automobile and woke up in the local hospital. His roommate was a young boy who developed a lung abscess from aspirating a piece of food. The boy was desperately ill. He had a high fever, coughed continuously, and brought up large globs of foul-smelling pus mixed with blood. No effective treatment was available. For 2 weeks, as his own condition was improving, Overholt lived with the brassy sound of a cough and the putrid smell of pus. One day the boy was wheeled out of the room to die elsewhere in the hospital. Overholt took the death of the boy hard. To make matters worse, he suspected that if the infected lung could have been removed or the pus drained his roommate might have lived. The thought haunted the first-year medical student and became a driving force behind his growing interest in maladies inside the chest. Indeed, soon after discharge from the hospital, he joined a project that resulted in the development of a two-stage technique of draining lung abscesses with an intercostal tube. Overholt was convinced that, had the method been available earlier, it could have saved his roommate's life. In later years, when he was criticized for bold pioneering practices, he would recall the young boy's agony and the results of his work on draining lung abscesses that might have changed the outcome. The connection served as a constant source of reassurance and incentive to forge ahead with his innovative approach to thoracic surgery.

In 1926, Overholt moved to Philadelphia to start his surgical training at the Hospital of the University of Pennsylvania, one of the topflight medical centers in the Western World. After the First World War, American medicine began to challenge Europe's traditional monopoly of excellence in medical research and training. The Hospital of the University of Pennsylvania was one of the leading centers in this race and achieved a world-class position. The staff included several world-renowned surgeons, and the wards offered an abundance of operative experience for trainees. Overholt's first rotation was on the Service of Chevalier Jackson. The broad clinical experience and the exposure to the inventor of the bronchoscope fueled his enthusiasm and intention to extend the horizons of thoracic surgery. Although his ward duties kept him fully occupied, he found time to work on projects outside his assigned responsibilities. Of the several studies he initiated during his residency Overholt's favored story was about a newly developed Burgess oxygen tent for the treatment of severe pneumonias. He was convinced that the system had the potential of improving on existing therapy and enlisted the help of the senior staff to buy a unit and try it on their patients. The tent was used under Overholt's supervision and credited with saving the lives of some of Philadelphia's industrial magnates from seemingly fulminant pneumonias. The grateful patients rewarded the young doctor by donating enough tents to supply the needs of the entire hospital. The project did not escape the attention of Overholt's mentors.

During his residency, Overholt's reputation grew steadily as an outstanding technician with rapidly maturing clinical judgment. In the second year of his surgical fellowship, George Muller, a senior attending surgeon, asked Overholt, instead of one of his associates, to lance an abscess on his arm and to dress the wound subsequently. The care provided by the resident must have impressed the senior staff man. The following year Overholt served as a fellow on Muller's service. In 1931 Dr Frank Lahey visited the Hospital of the University of Pennsylvania and saw Overholt in action assisting his chief. After Lahey returned to Boston he invited the young surgeon to join the Lahey Clinic. Overholt accepted but stipulated that in addition to his work in general surgery he would be free to pursue his interest in surgical problems of the chest.

During the 1920s progress in thoracic surgery had been gaining momentum steadily. Roentgenography of the chest was employed with rapidly increasing frequency. The use of intercostal tubes was also growing. Surgeons persisted with lobar resections of the lung in spite of an almost prohibitive operative mortality. In a few centers, endotracheal anesthesia was administered through uncuffed tubes. Overholt sensed the implications of this new technique for intrapleural operations. In spite of the impressive progress in the field, thoracic surgery was far from an accepted or desirable specialty, and surgeons were reluctant to limit their work to the chest. In Boston there were only three surgeons who practiced the controversial specialty of thoracic surgery.

In spite of a full schedule in general surgery at the Lahey Clinic, Overholt did not lose sight of the plight of the vast patient population suffering from pulmonary tuberculosis. Medical therapy was nonspecific and practically ineffective. The disease was chronic, debilitating, indolent, and frequently lethal. People suspected of harboring tuberculosis were not admitted to general hospitals but were isolated in sanatoria and languished for years in the empty hope that rest, sun, clean air, and good food would prevail over the infection. The surgical armamentarium was limited to thoracoplasty, but the procedure had been practiced in fewer than 20 centers in the entire country. Indications were confined to a few specific clinical subsets, the risk of the operation was high, and the outcome was unpredictable. Induced pneumothorax, the only widely practiced invasive therapy, was gradually being abandoned. Most surgeons ignored the tuberculous patient, but Overholt looked on the disease as a major public health problem and a surgical challenge of the first order. Most physicians, however, rejected any type of surgical approach to tuberculosis during the 1930s.

In spite of his meager experience with thoracic operations, Overholt was confident that he could master thoracoplasty. He convinced Dr Nathan Pillsbury, superintendent at the Boston suburban Norfolk Sanatorium, to refer 10 patients for thoracoplasty on a trial basis. All 10 survived the operation. Nine recovered completely and returned to an active life. This was a remarkable achievement for those days. News of the success with the "Norfolk Ten" spread rapidly in medical circles and established Overholt's reputation as a bold and excellent thoracic surgeon, willing to pioneer difficult operations in high-risk patients and produce impressive results. Physicians who had previously opposed thoracoplasty became advocates. Overholt was flooded with patients from all over New England. Because he could not admit his tuberculous patients to general hospitals, Overholt organized "saddle-back" surgical teams to take the operation to the patient in the various sanatoria of Massachusetts and Rhode Island. By 1935, he reported on one of the largest series of thoracoplasties (120 operations) with an enviable operative mortality of 2.5% [2]. The large experience with chest wall surgery provided an opportunity to master the technical intricacies of the procedure, to learn about the physiological disturbances associated with major surgical trauma, to perfect instruments, and to improve on techniques, but above all it prepared Overholt for his next major challenge. "When it came time for me to take the great leap into intrathoracic surgery, . . . I was as well prepared as I could be, short of having actually performed open chest surgery."

Removal of lung tissue along nonanatomic planes as well as anatomic lobectomy were reported sporadically during the first two decades of the twentieth century. In 1923, Graham could find 48 recorded cases of pulmonary resections for bronchiectasis, the most common indication for lobectomy in those days [3]. The operative mortality was 52%, and bronchial fistula developed in all survivors. In spite of the high risk of the operation, many desperately ill individuals looked to pulmonary resection as their only hope of escaping death or a miserable existence. The situation was poignantly described in 1922 by Howard Lilienthal, a leading thoracic surgeon of those days [1]:

> Patients have even threatened suicide if refused the chance of operation. . . . To refuse to operate on a wretched patient, otherwise incurable, merely because statistics may be unfavorable, seems hardly fair. . . . To have been the instrument of restoring one of these wretched people to blooming health after months or years of revolting illness with the constant fear of fatal pulmonary hemorrhage is the richest reward surgery can offer.

In 1933, with three successful lobectomies as his total experience with intrapleural operations, Overholt felt that he was ready to face the challenge of pneumonectomy. In his view, the major breakthrough operations of the past had been fueled more by courage and self-confidence than by firsthand experience. He thought that there was little additional information to be gained from others because only a handful of surgeons had success with pneumonectomy and the experience of each was limited to 1 or 2 cases. In Overholt's estimation he possessed the requisites to join the company of the frontline frontier surgeons. The task he faced was formidable. Removal of an entire lung in those days was viewed as a dangerous operation with a lethal threat to homeostasis. The greatest fear was that ligation of a major pulmonary arterial trunk would precipitate immediate circulatory collapse similar to that associated with massive pulmonary embolization. There was also concern that removal of an entire lung would destabilize the mediastinum and lead to fatal cardiorespiratory failure. Finally, it was anticipated that the fluid that fills the residual pleural space would in some way be harmful.

Despite the anticipated hazards the desire to meet the challenge of pneumonectomy was steadily mounting. Although there were no survivors from the few attempted procedures before 1931, the projected benefits made the operation ever more inviting. Some infections claimed an entire lung and it was hoped that getting rid of the source would cure the disease. Furthermore, it was widely believed, in the early years of pulmonary surgery, that an entire lung must be resected for adequate treatment of bronchogenic carcinoma because lesser operations would not extirpate the malignancy.

In an attempt to reduce the risks of pneumonectomy, the pioneering surgeons resorted to a staged approach. They postulated that staging would not only attenuate a massive onslaught on cardiorespiratory equilibrium and facilitate a gradual physiologic adaptation but would also shorten the duration of each procedure and diffuse the magnitude of the surgical trauma. Preoperative thoracoplasty and artificial pneumothorax were employed with the anticipation that these collapse maneuvers would facilitate gradual adaptation to the cardiorespiratory disturbances created by removal of a whole lung. The phrenic nerve was interrupted before or during the pneumonectomy to reduce the size of the residual pleural space. The resection itself was staged into strategically feasible and physiologically tolerable units such as exploratory thoracotomy to determine resectability, freeing the lung from adhesions, ligation of the hilar pedicle with or without simultaneous removal of the lung, and postresection thoracoplasty to reduce the size of the residual space. If the lung was left behind after mass ligation of the hilar pedicle, the devitalized pulmonary tissue would eventually slough spontaneously. Although the extent of each stage was frequently planned preoperatively, the actual magnitude of the procedure was usually dictated by the intraoperative cardiorespiratory response of the patient.

Gluck [4] demonstrated in 1881 that it was possible to obtain survival from pneumonectomy in experimental

Table 1. Chronology of Successful Pneumonectomies

Surgeon	Date of Operation	Disease	Age of Patient (y)	Side	Staging
Nissen	7/7/1931	Suppurative	12	L	M
Haight	11/8/1932	Suppurative	12	L	M
Graham	2/27/1933	Cancer	48	L	S
Archibald	7/71933	Sarcoma	31	L	S
Rienhoff	7/24/1933	Tumor, benign	3	L	S
	11/3/1933	Tumor, malignant	24	L	S
Overholt	11/13/1933	Cancer	33	R	S

L = left lung; M = multiple; R = right lung; S = single.

animals. It took, however, another 30 years before Kuemmel in 1911 attempted the procedure on a man [3]. The patient died of heart failure and pneumonia 6 days after the operation. Over the next 20 years there were sporadic attempts at pneumonectomy by Meyer, Lilienthal, Archibald, Hinz, Ivanissevich, and perhaps others, but none of these patients survived [1, 3]. Death was commonly caused by massive hemorrhage or respiratory insufficiency due to failure of the mass ligature on the pulmonary pedicle. Exsanguination due to a slipped ligature on the pulmonary vessels was referred to as "white death" whereas asphyxiation from disruption of the bronchial closure was described as "black death."

The first recorded successful pneumonectomy in the world was performed in 1931 by Nissen in Germany on a 12-year-old girl with severe bronchiectasis and a parenchymal abscess that ruptured into the pleural space (Table 1). The operation was staged into thoracoplasty with phrenic nerve interruption followed by lysis of pleural adhesions with mass ligation of the pulmonary pedicle. The necrotic lung sloughed away after 14 days. The patient was doing well 7 years later [5].

During the 2 years following Nissen's left pneumonectomy five similar successful resections were reported (see Table 1). From this sequence, Graham earned the distinction of performing the first successful left pneumonectomy for cancer of the lung and also the first successful one-stage operation [6]. Archibald and Rienhoff, almost simultaneously, succeeded with dissection and division of the hilar components separately instead of using the mass ligature technique [1, 7, 8]. These two surgeons introduced the fundamental elements of the contemporary techniques and have been called fathers of modern pulmonary resection. Survival of a right-sided pneumonectomy, however, remained to be achieved.

In 1933 Overholt attended the Sixteenth Annual Meeting of the American Association for Thoracic Surgery in Washington, DC, and was impressed by Graham's detailed account of the left pneumonectomy he had performed a few months earlier [6]. Graham actually brought along and showed the surgical specimen preserved in a jar of formaldehyde. After hearing Graham's presentation Overholt returned to Boston convinced that he could succeed in performing the operation on the right side.

In November 1933, Overholt saw a 33-year-old woman with cough, fever, and weight loss. Chest roentgenography revealed a 4.5-cm discrete shadow near the right hilum. Bronchoscopy disclosed an obstructive mass in the right lower lobe bronchus. Even though the biopsy material showed chronic inflammation, Overholt thought that the lesion was cancerous and would be best treated with a pneumonectomy. He hesitated briefly because he was aware that the 11 previous known attempts at right pneumonectomy failed to produce a single survivor. On November 13, 1933, Overholt explored the patient through an anterolateral thoracotomy. He found a cancerous lesion and performed a right pneumonectomy in a single stage using the mass ligature technique. The patient survived. She represented the first successful right pneumonectomy in the world. Details of the operation were presented at the Seventeenth Annual Meeting of the American Association for Thoracic Surgery in June 1934 and were reported in the *Journal of Thoracic Surgery* [9].

Approximately 26 years after the operation Overholt received a frantic midnight call from his patient and drove 90 miles to her home. She was in severe respiratory distress. A bronchoscopy was performed in the living room. There was an inspissated plug in the left main bronchus that had obstructed almost completely the lumen. It was removed through the bronchoscope. Relief was dramatic and immediate. The patient lived for another 3 years and died 29 years after her right pneumonectomy.

Between 1933 and 1936 Overholt performed 22 additional pneumonectomies with an operative mortality of 22%. During the same period he could track 104 recorded cases worldwide with an operative mortality of 47% [10]. In the early experience mass ligation of the hilus was practiced most commonly, but gradually separation of the hilar components became the accepted technique. Similarly, the trend gravitated from a multistage approach to a single procedure. Gradually, pneumonectomy evolved into a common operation, performed in one operative session with dissection and control of individual components of the hilum but without auxiliary collapse maneuvers.

After the breakthrough one-stage right pneumonectomy, the 32-year-old Overholt continued his pioneering work on surgical treatment of pulmonary tuberculosis, bronchiectasis, and lung cancer [1, 3]. He left the Lahey Clinic in 1938 with some hesitation because he was concerned about having enough work in a practice limited to thoracic surgery. The anxiety proved unwarranted. Referrals were abundant. Overholt performed and reported on large numbers of thoracoplasties, pulmonary resections, and extrapleural pneumothoraces. His creative energies were focused on improving operative techniques and advancing new procedures. He was regarded by his contemporaries and residents as a bold and innovative surgeon as well as a master technician with uncanny clinical judgment. Among his many achievements, Overholt contributed heavily to the development of segmental resection of the lung and employed it widely and with great skill [11]. He reported the first case of bilateral segmentectomy for bronchiectasis [12]. A book by Overholt entitled *The Techniques of Pulmonary Resection*, published in 1949, became a classic [13]. With the introduction of antibiotics and antituberculous drugs for the treatment of surgical infections of the lung, Overholt switched his energies to tackle pulmonary cancer and led the field of surgery for bronchogenic carcinoma. He also introduced the prone position for pulmonary surgery to prevent spillover to the contralateral lung. The operation was performed on a special operating table designed by Overholt. It was used widely before the advent of the double-lumen endotracheal tube and the availability of antibiotics. In the Soviet Union between 1962 and 1967 40% of all thoracic operations were performed in the Overholt prone position [1].

Overholt pursued his second passion, the campaign against smoking, with the same vigor as he did his pioneering work in thoracic surgery. At the very beginning of his career, in the early 1930s, Overholt noted that operative morbidity and mortality were lower in the few sanatoria where smoking was prohibited than in others where the habit was permitted. Nonsmokers had a smoother and quicker convalescence from thoracic surgery than smokers. He was also impressed by his observation that smokers had darker, stiffer, and less easily deflatable lungs than nonsmokers [14]. There was little question in his mind that cigarettes inflicted heavy damage on the lung. He shared his concern about the ill effects of smoking freely with his colleagues during conversations as well as through presentations at medical meetings across the country. The reaction of the profession ranged from skepticism to ridicule. Undaunted, Overholt embarked on a campaign to educate, warn, and convince about the dangers of smoking. He spoke before grammar and high school, college, church, and medical audiences. Alton Ochsner was one of the few prominent surgical colleagues who joined in the battle. Organized medicine and voluntary health organizations did not share Overholt's concerns or support his efforts. A 1948 editorial in the JAMA on cigarette advertising stated that . . . "there does not seem any preponderance of evidence that would indicate the abolition of the use of tobacco as a substance contrary to the public health" [15]. Whereas the antismoking movement was small and without resources, the 80 billion dollar tobacco industry, backed by powerful legislators, flooded advertising boards and the media with an aggressive campaign. In his battle against the tobacco interests Overholt portrayed himself as a dwarfed David facing an overgrown Goliath.

After almost two decades of frustration, help came in the form of a 1950 article in the *Journal of the American Medical Association* by Wynder and Graham [16] reporting that out of 650 men with lung cancer studied, more than 95% had been smoking for at least 20 years. Spurred by this publication, the prominent heart surgeon, Dwight Harken, joined the antismoking movement [14]. As the evidence about the risks of smoking was pouring in, the American Medical Association banned cigarette advertising from all of its publications. In 1953, the American Cancer Society reported that the incidence of lung cancer in men was rising at an alarming rate. Cigarette consumption declined during 1953 and 1954. A concerned behemoth responded with the formation of a generously financed Tobacco Industry Research Council to support projects that might counter the steadily increasing number of adverse scientific reports about smoking. In 1964, a blue ribbon commission appointed by Surgeon General Luther Terry concluded that cigarette smoking was a primary cause of lung cancer and was linked to emphysema, chronic bronchitis and cardiovascular diseases [17]. A 20% decline in cigarette smoking followed during the ensuing year. Finally, after a long, seemingly futile struggle and against overwhelming odds the antismoking movement began to prevail. The long-standing inertia in the war against smoking was broken.

During the next 25 years the antismoking crusade gained momentum steadily. Individual physicians, the collective medical establishment, and voluntary health organizations joined governmental agencies in a concerted effort to educate, warn, and advise the public and to regulate the habit in public settings. New legislation mandated the display of a warning about the harmful effects of smoking on individual packages of tobacco products and barred the sale of cigarettes to minors. Smoking was prohibited in a steadily increasing number of designated public locations, and the areas where the habit is allowed have been shrinking gradually. The use of tobacco has steadily declined. In 1955, 52% of American males smoked but by 1985 the figure had fallen to 33% [14].

Just as he led the fight when the antismoking crusade was not popular, Overholt was in the forefront when the movement gained public support. He continued with extensive lecturing and helped recruit prominent medical and civic leaders, such as the cardiologist Paul Dudley White and US Senator Maureen Neuberger. In establishing an infrastructure to carry on the mission Overholt turned to a dual approach consisting of prevention and treatment. His efforts to launch antismoking organizations included participation in the formation of Group Against Smoking Pollution (GASP) and Action on Smoking and Health (ASH) to promote prevention and Smoker's Anonymous to facilitate treatment. Overholt testified before congressional committees and in liability suits against tobacco companies. One of his 1964 publications illustrates his concern and eloquence [18]. It qualifies as a classic in the annals of medicine:

> Now we are involved with perhaps the greatest public health problem ever known. The world wide cigaret habit has had such an insidious development and has become so firmly entrenched that we still have no proper perspective of it. Pulmonary cancer, emphysema and cor pulmonale are causally related. Other degenerative diseases are aggravated by it; these include coronary spasm and thrombosis, circulatory disturbances, peptic ulcer and so forth. Quantitatively, the resulting wide devastation is far greater than smallpox or plague ever was. . . . The cigaret death, however, hits the head of the family, the wage

> earner and the leader. It punches a hole in the great interlocking economic framework on which our modern complex life depends. . . . The worlds of sport, medicine, communications, entertainment, the military, and others have paid human sacrifice to the cigaret.
>
> In contrast, advertising has created a smoking super-race which must be dethroned. Coaches have always known instinctively that cigarets diminish full physiologic performance, yet Saturday's heroes tell our young to light up. On the stage and screen, not only sophisticated good guys but also the virile bad guys maintain a perpetual semaphore of smoke.
>
> Who will be the emancipator? . . . In this war of attrition which is going to last at least a generation, the medical profession must be the leader, the emancipator. We should take the initiative now and we must not lose it.
>
> How can we emancipate? We must approach legislation without fanaticism. Certainly, vending machines must be abolished to cut off the supply to the ten and twelve year olds. A substantial tax raise should not be difficult to enact since in this case it can be done righteously, and the primary target will be school children most of whom are poor and voteless. Brainwashing by television and phony advertisements in the press should be curbed. There will be vigorous fights by the industry against such acts, but they should eventually pass if we continually make it clear that voting against them is like voting for pyromania [18].

Overholt was blessed with a long and productive life. His wife, Polly, had been a close companion, source of love and inspiration as well as head of the Overholt household during the long hours of his absence. His three children, Jane, Hollis, and Ann, five grandchildren, and one great-grandchild had been an ever-broadening source of pride and pleasure. Richard Overholt's contributions to his patients, profession, and society were recognized during his lifetime through simple heartfelt thanks, respect of his colleagues, appointments to positions of trust, honor, and influence as well as through a host of other tributes. The sincerity of his convictions in the healing power of surgery was tested in his eighties when he needed two major operations and confided to friends that he considered himself lucky to be a suitable candidate. Indeed, Overholt underwent and weathered a colectomy and coronary artery bypass grafting without hesitation. In spite of setbacks, his bright spirit kept him active in his dual call as a thoracic surgeon and antismoking activist for almost six decades, well into his eighties. At the age of 89 Overholt ran an office practice and, although he had discontinued independent surgery 10 years earlier, he never left his principal source of inspiration and continued with his presence in the operating room through assisting other surgeons. His commanding role in the antismoking movement was acknowledged through a feature series in the *Boston Globe Sunday Magazine* with a telling picture of Dr Overholt on the cover (Fig 1). Richard Overholt died on July 16, 1990. He will be remembered as one of the bold and creative pioneers during the explosive growth of thoracic surgery and a visionary crusader against the perils of smoking. His death took away one of the very few living witnesses and participants in the genesis of thoracic surgery and in the origins of the antismoking crusade.

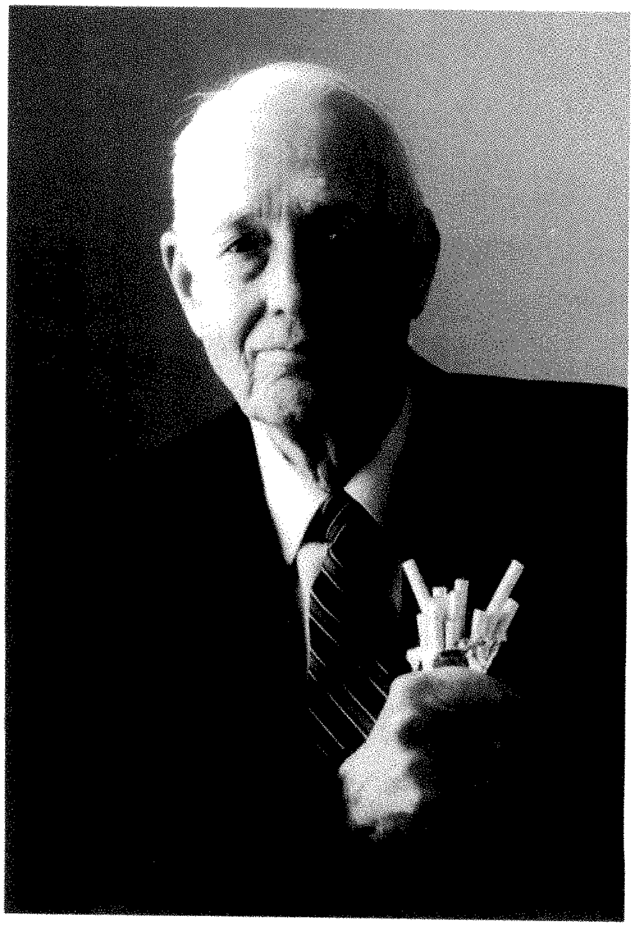

Fig 1. Richard Overholt on the cover of the Boston Globe Sunday Magazine *of May 4, 1986.*

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1994 may begin the recertification process in 1992. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is May 1, 1992. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Life-Threatening Postoperative Junctional Ectopic Tachycardia

Paul W. Braunstein, Jr, MD, Robert M. Sade, MD, and Paul C. Gillette, MD

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Junctional ectopic tachycardia developed in an infant after intraatrial repair of transposition of the great arteries. He failed to respond to medical management and, in moribund condition, underwent His bundle cryoablation. He survived and ultimately did well. Junctional ectopic tachycardia is not uncommon after open heart operations in children and may be lethal. Its genesis, diagnosis, and treatment are now well enough understood to allow successful treatment of nearly all patients.

(Ann Thorac Surg 1992;53:726–8)

Rapid junctional ectopic tachycardia (JET) develops within hours of operation in approximately 5% of children undergoing open heart operations, and it can be lethal [1, 2]. The arrhythmia is self-limited if hemodynamic consequences can be controlled. Nevertheless, there is substantial risk of death with conventional antiarrhythmic treatment. We present a patient with JET unresponsive to conventional medical treatment who underwent radical therapy, His bundle ablation, to prevent imminent death.

Case Report

In 1985, a 4-month-old boy with d-transposition of the great arteries underwent an elective Senning procedure. The heart rate immediately after removal from bypass was 180 beats/min, and it gradually increased to 240 beats/min with atrioventricular dissociation and a junctional ectopic pacemaker (Fig 1). After initial hemodynamic stability, blood pressure and urinary output began to decline, and peripheral perfusion deteriorated.

Initial treatment of JET included discontinuation of dopamine and sequential administration of propranolol and digoxin intravenously and flecainide by nasogastric tube. Attempts at overdrive atrial pacing were unsuccessful. Other attempts to control the heart rate included surface cooling to a core temperature of 35°C, maintaining serum potassium level greater than 4.0 mEq/L and ionized calcium level greater than 1.2 mmol/L by administration of these ions, and inducing mild respiratory alkalosis. When these failed to control JET, intravenous propafenone administration was initiated.

Hemodynamics remained poor and the patient became moribund, with systolic blood pressure less than 60 mm Hg, little urine output, and cold, pulseless extremities. Thirty-six hours after the Senning procedure, he was returned to the operating room and placed on cardiopulmonary bypass, and the sites of the atrioventricular node and the His bundle were frozen with a 3-mm cryoprobe at −70°C. Permanent atrial and ventricular epicardial leads were implanted, in addition to the temporary leads already in place. The rhythm was then junctional with complete atrioventricular block and a heart rate of 120 beats/min. Acute tubular necrosis persisted over the next 3 days, then improved.

The patient was removed from the ventilator on the ninth day after ablation. A permanent DDD pacemaker was implanted on the twentieth day. He was discharged home 4 days later.

Cardiac catheterization 2 years after operation demonstrated excellent hemodynamic result of the repair. Electrophysiological study demonstrated normal sinus node function, and atrioventricular conduction was blocked below the His spike. The patient has experienced minor developmental delay, but his overall health remains excellent.

Discussion and Review of Literature

Junctional ectopic tachycardia is a life-threatening postoperative arrhythmia in children. It occurs most often after repair of tetralogy of Fallot, but it can occur after operation for any congenital cardiac lesion. Other factors that may predispose to JET include incomplete repair, long aortic cross-clamp time, young age at repair, and inadequate myocardial protection [1, 2].

Diagnosis

The key to treatment is early diagnosis before low cardiac output associated with the arrhythmia becomes established. A high level of suspicion of JET should arise when a gradually rising heart rate is seen with atrioventricular dissociation (ventricular rate usually faster than atrial rate), short PR interval, or absence of P waves. High-quality electrocardiography should be done immediately.

The diagnosis is best confirmed with an atrial electrogram (a rhythm strip with an atrial pacing wire connected to the V_1 input lead, lead selection based on clearest demonstration of P waves). The QRS complex is usually unchanged from before the arrhythmia and does not change with atrial pacing. The diagnosis of JET is further

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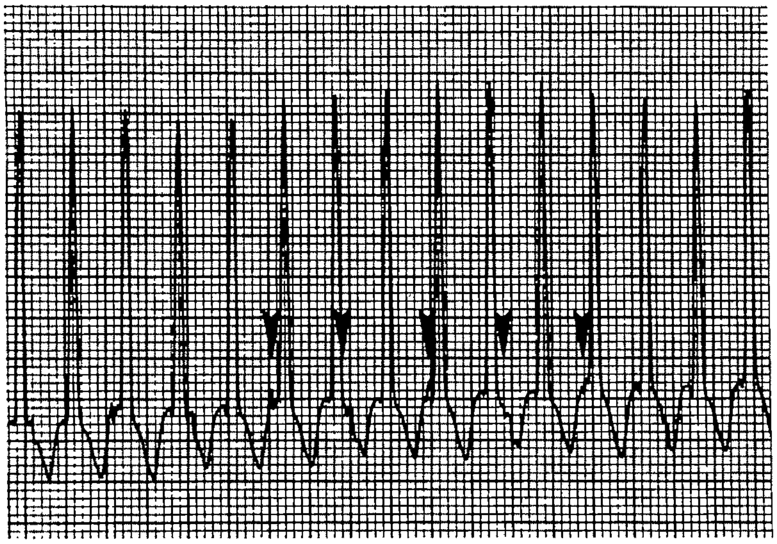

Fig 1. Electrocardiogram demonstrating junctional ectopic tachycardia: atrial rate is 155 beats/min, ventricular rate is 234 beats/min. Several consecutive P waves are denoted by arrowheads.

suggested by lack of effectiveness of atrial or ventricular overdrive pacing or of electrical cardioversion.

Etiology

The underlying arrhythmogenic mechanism is probably enhanced automaticity in the bundle of His [3, 4]. Automaticity of these tissues is increased by sympathomimetic and vagolytic influences and by rising temperature.

We have been interested in this arrhythmia for some time. To clarify the clinical milieu in which it develops, we have informally reviewed records of about 20 patients with JET seen at this institution since 1984 and have observed several factors that may predispose to its genesis [5]. Certain drugs frequently used in pediatric cardiac patients perioperatively, such as pancuronium, barbiturates, and meperidine, are vagolytic and may increase heart rate.

Sympathomimetic agents such as isoproterenol, dopamine, dobutamine, and epinephrine were often being administered to these patients. Whether the arrhythmia was caused by these inotropic agents or by the low cardiac output state that prompted administration of the agents is speculative. Great care must be used when administering these agents to patients with JET.

Antiarrhythmic agents such as procainamide and verapamil are vagolytic and can increase the rate of tachycardia [6]. Although β-blocking agents may slow the heart rate, they may also decrease cardiac output.

Vasodilating agents such as amrinone and nitroprusside were often being administered to our patients with JET. They should be avoided because they may reflexively increase the heart rate. Hypocalcemia (ionized calcium level less than 1.2 mmol/L), hypomagnesemia (less than 1.9 mg/dL), and hypokalemia (less than 4.0 mEq/L) were all likely to be present in patients with JET.

Treatment

Because JET is usually of limited duration, the main early objectives of its treatment are to increase cardiac output, decrease heart rate, and decrease tissue oxygen demand. When the diagnosis is made, certain maneuvers should be implemented immediately. Hypothermia is the cornerstone of treatment: hypothermia is known to suppress automaticity of the heart and lead to bradycardia, so the child's core temperature should be immediately lowered to 33° to 35°C [7]. This maneuver both slows the heart rate and decreases the body's utilization of oxygen and need for cardiac output. We achieve cooling by surrounding the patient with ice bags after sedation and paralysis (morphine or fentanyl, and metubine or vecuronium; all have minimal chronotropic and hemodynamic effects). Cooling blankets may also be used.

All metabolic abnormalities, especially hypokalemia, hypocalcemia, and hypomagnesemia, should be vigorously corrected, bringing the potassium level to more than 4.0 mEq/L, ionized calcium level to more than 1.2 mmol/L, and magnesium level to the 1.5 to 2.0 mg/dL range.

Hypovolemia may contribute to tachycardia, so it should be corrected by appropriate fluid replacement. To avoid tachycardic effects of anemia, the hematocrit should be maintained greater than 0.35. Atrial pacing at a rate just above the junctional rate may improve cardiac output by an average of 10% to 15%.

Digoxin increases contractility and cardiac output and is vagotonic, so it should be administered at an optimal dose after the potassium level is within the normal range [1]. If the patient appears to have adequate cardiac output, a β-blocker (for example, esmolol, because of its short half life) may be judiciously administered intravenously, although in general we try to avoid these drugs.

Antiarrhythmic agents usually decrease vagal tone, depress myocardial contractility, decrease systemic vascular resistance, and are ineffective in ameliorating JET. For these reasons, we avoid conventional antiarrhythmics. If the tachycardia is not improving or the patient's clinical state is deteriorating despite the above measures, type IC antiarrythmic agents (flecainide, encainide, propafenone) may be tried. They have been found effective in treating some automatic arrhythmias [8].

We now use propafenone intravenously. It is still investigational, and, in addition to its antiarrhythmic effects, is known to decrease cardiac output, increase systemic vascular resistance, and increase left ventricular end-diastolic pressure. The drug must be used with caution.

If propafenone fails to control the arrhythmia and the patient's condition continues to deteriorate, we would finally offer emergency ablation of the His bundle. The procedure can be performed in the cardiac catheterization laboratory by transvenous fulguration [9] or radiofrequency ablation [10], or it can be performed surgically [11]. We chose surgical cryoablation for our patient because electrical fulguration by catheterization may produce high enough intracardiac pressures to rupture fresh suture lines and because the bundle of His is relatively inaccessible by catheterization after the Senning operation (the coronary sinus is in the physiological left atrium). Surgical methods described to ablate the His bundle include ligation, division, electrocautery, and cryoablation [11]. Upon completion of the operation, permanent atrial and ventricular wires should be placed in preparation for permanent DDD pacing.

Our experience with JET over the past several years has led to the development of a protocol that we institute immediately in all patients in whom the arrhythmia develops postoperatively (Appendix 1). The implementation of this protocol usually prevents the arrhythmia from feeding upon itself and producing progressive clinical deterioration. Since this protocol was instituted 7 years ago, none of the several patients we see each year with JET has died. The only patient who came near to death was the one we report here. When medical management has failed and irreversible shock seems imminent, His bundle ablation is a radical but reasonable therapeutic alternative.

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Appendix 1. Junctional Ectopic Tachycardia Protocol

1. Keep core temperature low (33° to 35°C; lower if needed)
2. Keep K^+ level at upper normal range (>4.0 mEq/L)
3. Keep Ca^{2+} (1.14 to 1.29 mmol/L) and Mg^{2+} (1.4 to 1.9 mg/dL) levels at upper normal range
4. Avoid all drugs except those below
5. Sedate with morphine (0.1 mg/kg) or fentanyl infusion (0.01 to 0.04 $mg \cdot kg^{-1} \cdot h^{-1}$)
6. Paralyze with vecuronium (0.1 mg/kg loading dose, then 0.03 mg/kg every 30 to 60 minutes as bolus or infusion)
7. Ventilate to keep arterial blood pH between 7.45 and 7.50
8. Optimize digitalis dose
9. Optimize blood volume and hematocrit (0.35 to 0.40)
10. Use β-blockers if cardiac output is adequate (use cautiously: negative inotropic effect)
11. Pace atrium if possible to maintain atrioventricular synchrony
12. Use propafenone cautiously
13. Finally, if all else fails, ablate bundle of His

Practice Guidelines in Cardiothoracic Surgery

During the last 10 years, members of our specialty have been fielding, on an individual and on a collective basis, requests regarding standards of care as they relate to our patients. These requests have come mainly from third-party payors on a national level, as well as private carriers, and also from medicolegal committees within our specialty organizations. The Council of The Society of Thoracic Surgeons, after much deliberation involving many council meetings, ultimately decided that these requests were legitimate and that a carefully structured response from our specialty was indeed indicated. From the outset, it was decided that these documents should represent the opinions of our specialty as completely as possible and, therefore, the active participation and support of the other three major thoracic societies (the American Association for Thoracic Surgery, the Western Thoracic Surgical Association, and the Southern Thoracic Surgical Association) have been solicited.

The committee and subcommittees formed as a result of this action of the Council of The Society of Thoracic Surgeons have met on many occasions and have had considerable deliberations concerning these matters. First of all, a title for these documents was thoroughly discussed; the use of the word "guidelines" seemed most appropriate and perhaps "minimal guidelines" would be even more appropriate. There was a clear understanding among the participants that this was not to be an effort to provide a textbook description of each procedure with a detailed analysis of every facet of patient care and outcome analysis, but rather it was to be a simple description of those things that are normally anticipated in developing the indications for surgery, as well as simple statements regarding those things to be anticipated before, during, and after the operative procedure in the care of the patient. It also was agreed that an attempt would be made to provide some broad-range outcome statements. It was also understood that, even though this work product could be entitled "minimal guidelines," some of the items identified might not be included in the care of an individual patient. Further, it was clearly understood that many other items might logically and appropriately be included in patient care and not included in these minimal guidelines.

Finally, and perhaps most importantly, it was agreed upon that this work product should be a "living document" and that frequent review and revision would be a part of the work intended. With the rapid advance of technology and patient care techniques, this final point is essential. Because of the volume of this effort, it will not be published in total form, but rather in the various elements of our specialty as the work product is completed and publication is appropriate. Because of the nature of the presentation of this material to thoracic and cardiovascular surgeons, it is clearly understood that revision of the first published portions of these documents may well be indicated prior to completion of the coverage of our specialty. Because of this, comments and suggestions regarding these guidelines are encouraged and solicited and should be addressed to the management of The Society of Thoracic Surgeons. It is our commitment to act upon these comments and suggestions and to revise and maintain this living document in a timely fashion.

George G. Lindesmith, MD
President, The Society of Thoracic Surgeons
1988–1989

Background

During his tenure as President of The Society of Thoracic Surgeons, George G. Lindesmith appointed the Ad Hoc Committee for Cardiothoracic Surgical Practice Guidelines. The original committee composition was as follows:

GEORGE C. KAISER, MD, CHAIRMAN, St. Louis
THOMAS D. BARTLEY, Pueblo, CO
JOSEPH S. COSELLI, Houston
JAMES A. DEWEESE, Rochester, NY
THOMAS B. FERGUSON, St. Louis
RICHARD G. FOSBURG, La Jolla
ROBERT H. JONES, Durham
GEORGE G. LINDESMITH, Los Angeles
KEITH S. NAUNHEIM, St. Louis
D. GLENN PENNINGTON, St. Louis
MARVIN POMERANTZ, Denver
W. GERALD RAINER, Denver
ROBERT M. VANECKO, Chicago

The organizational meeting of the Committee was held in Boston, Massachusetts, on May 8, 1989. During this and subsequent meetings, the guideline format and its degree of complexity were discussed extensively. It was recognized that practice guidelines were being constructed by many organizations, each with its own agenda and requirements. Therefore, guidelines varied in detail and complexity according to the perceived needs of the constituency. Furthermore, it was noted that there are no universally accepted guidelines for writing practice guidelines. However, to help the STS committee formulate its plan, guidelines already in existence or being developed were collected from other medical and peer review organizations, third-party payors, and both federal and state governments. This information was invaluable in assisting the Committee in arriving at its decisions regarding the structure and complexity of cardiothoracic surgical practice guidelines. After careful and extensive deliberation, it was decided to approach Practice Guidelines under the following rubrics:

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1. **The guidelines would be procedure-oriented.** Appropriate CPT codes were to be indicated. This would allow appropriate identification of each procedure as it would be coded in the revised CPT-4 code book. The Society's CPT-4 Advisory Committee, under the Chairmanship of Sidney Levitsky, was assisting in the revision of the cardiothoracic surgical codes which in many instances were out of date or in which codes were entirely lacking for procedures such as thoracic organ transplantation and left ventricular assist device insertion. Furthermore, listing of the procedure and diagnostic codes would assist members in their practice and other bodies in identifying the exact procedure being performed.
2. **The field of cardiothoracic surgery would be divided anatomically and associated pathologic processes in each area would be addressed.** Although the guidelines were to be procedure oriented, the field of cardiothoracic surgery was organized along anatomic and pathologic lines. Organization of the guidelines in this manner was decided upon to allow ease of categorization and implementation. This apparent ambivalence was accepted to facilitate guideline development, yet encompass the entire field of cardiothoracic surgery. Although some organizations that developed practice guidelines had struggled with this apparent dichotomy between disease entities and procedures, the Committee felt its approach was practical and would expedite this complex process.
3. **The criteria published by the American College of Obstetricians and Gynecologists* would be used as the model for the outline of the areas to be addressed for each Practice Guideline.** Their outline is:

    Procedure
    Indication
    Confirmation of Indication
    Action Prior to Procedure
    Contraindications

    Additions were made to this outline to address aspects not included in that outline and to make it more compatible with our needs. The subsequent headings decided upon by the Committee were:

    Diagnosis
    Procedure
    Indication
    Confirmation of Indication
    Relative Contraindications
    Actions Prior to Procedure
    Actions During Procedure
    Actions Following Procedure
    Outcome
    References

It was decided that cardiothoracic surgical textbooks would be the references of choice. There were many reasons for this decision, not the least of which was that these would represent the generally accepted view in the cardiothoracic surgical community, and only a few references would be required, thereby avoiding extensive and cumbersome bibliographies. For newer procedures for which textbook references were incomplete or unavailable, it was agreed that appropriate references from the cardiothoracic surgical literature would be supplied.

In view of the increasing emphasis by many upon outcome, it was agreed to include some estimate of expected outcome for each procedure.

Subcommittees for each cardiothoracic surgical category were appointed with a member of the Ad Hoc Committee as chairman of the subcommittee. These subcommittees and their membership are as follows:

1. Ischemic Heart Disease

    ROBERT H. JONES, CHAIRMAN
    GERALD M. LAWRIE
    WEI-I LI
    BRUCE W. LYTLE

2. Valvular Heart Disease

    THOMAS D. BARTLEY, CHAIRMAN
    JOSEPH M. CRAVER
    ROBERT A. GUYTON

3. Thoracic Aortic Disease

    JOSEPH S. COSELLI, CHAIRMAN
    E. STANLEY CRAWFORD
    RANDALL B. GRIEPP
    NICHOLAS T. KOUCHOUKOS
    D. CRAIG MILLER

4. Chest Wall, Diaphragm, Mediastinum, Pericardium

    THOMAS B. FERGUSON, CHAIRMAN
    LARRY R. KAISER
    KEITH S. NAUNHEIM
    CHARLES L. ROPER
    WILLIAM F. SASSER

5. Esophageal Disease

    ROBERT M. VANECKO, CHAIRMAN
    ROBERT J. GINSBERG
    ALEX G. LITTLE
    MARK B. ORRINGER

6. Bronchopulmonary Disease

    RICHARD G. FOSBURG, CHAIRMAN
    JOHN R. BENFIELD
    RICHARD M. PETERS
    THOMAS W. SHIELDS

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* Quality Assurance in Obstetrics and Gynecology, 1988 Edition, The American College of Obstetricians and Gynecologists, 409 12th St SW, Washington, DC 20024-2188.

7. Transplantation (heart, lung, heart-lung) and Heart Assist Devices

D. GLENN PENNINGTON, CHAIRMAN
WILLIAM A. BAUMGARTNER
A. MICHAEL BORKON
JACK J. CURTIS
VERDI J. DISESA
J. KENT TRINKLE

8. Electrical Problems (pacemakers, arrhythmias, AICD)

MARVIN POMERANTZ, CO-CHAIRMAN
W. GERALD RAINER, CO-CHAIRMAN

9. Congenital Heart Disease

GEORGE G. LINDESMITH, CHAIRMAN
JEFFREY M. DUNN
HILLEL LAKS
WINFIELD J. WELLS

James A. DeWeese, MD, serves as liaison between the cardiothoracic surgical organizations and the vascular surgical organizations, the North American Chapter of the International Cardiovascular Society, and the Society for Vascular Surgery. These vascular surgical organizations are developing practice guidelines for vascular surgery. This method of cooperation has been adopted to avoid reduplication of effort.

Each subcommittee was charged with the development of guidelines for that category of cardiothoracic surgical practice. In rare instances a procedure might be potentially addressed by more than one subcommittee. Any possibility for overlap was resolved by the parent committee. As an initial effort, each subcommittee was requested to develop guidelines for three of the most commonly performed procedures in its area of expertise. These practice guidelines were then reviewed and critiqued by the entire Ad Hoc Committee and all subcommittees. After refinement, the final results were submitted to the Council of The Society of Thoracic Surgeons for approval. It was anticipated that this complex ratification process might develop snags. Therefore initially, the introductory, preoperative evaluation, and institutional requirement sections along with guidelines for nine procedures were submitted for approval. It was anticipated that any potential problems with this review process that arose could then be resolved making ratification of future guidelines easier. Because in any extensive and complex review process as outlined there might be some differences of opinion, it was proposed that the Council of The Society of Thoracic Surgeons would be the final arbiter. The goal of this review process is to achieve consensus, but at the same time recognize that practice guideline development is, and always will be, a dynamic process.

It was decided that the first iteration of the guidelines be published every few months in *The Annals of Thoracic Surgery*. On the following pages are the first set of practice guidelines and the introductory, preoperative evaluation, and institution requirement sections. It is anticipated that eventually guidelines covering the entire specialty will be collated and published as a separate document. It should be emphasized that one of the most important aspects of this process is that these guidelines will require continual modification and revision as clinical cardiothoracic surgical practice changes.

I would like to thank the members of the Ad Hoc Committee and of each subcommittee for their effort and excellent cooperation.

George C. Kaiser, MD
Chairman, Ad Hoc Committee for Cardiothoracic Surgical Practice Guidelines

Introduction

The following sections provide basic practice guidelines for those individuals qualified in the specialty of cardiothoracic surgery. Although the practice of medicine requires a strong scientific foundation, medicine is also an art requiring both intuitive skills and good judgment. Occasionally, objective decisions concerning patient management must be modified depending upon such factors as individual patient characteristics or other associated factors. Such cognitive functions are an integral and essential part of the practice of cardiothoracic surgery with regard to preoperative patient evaluation, selection of operative procedures, and postoperative patient care until the patient has recovered. The ability to modify the process as needed for the greater benefit of the patient is vital if an optimal outcome is to be achieved for each patient. These intuitive and cognitive skills are essential to the successful practice of cardiothoracic surgery and must be applied in every phase, frequently requiring modification of the patient's care from preoperative preparation to discharge planning. These intellectual abilities are developed, sharpened, and maintained by constant exposure to patients in a clinical setting. In addition, the practitioner must update his or her fund of scientific information by journal review, attendance at scientific meetings and postgraduate seminars, as well as by consultation with colleagues both inside and outside of the specialty of cardiothoracic surgery.

Because guidelines are but one aspect in the ever-evolving field of cardiothoracic surgery, it is anticipated that these guidelines must be modified frequently to keep pace with the advances. As a background upon which practice guidelines will be developed, it is pertinent to delineate the extent of expertise encompassed by the specialty of cardiothoracic surgery. This has already been done.

> Scope of Thoracic Surgery[†]
>
> The thorax or chest extends from the neck to the abdomen and contains the principal organs of the circulatory and respiratory and upper gastrointestinal systems. The specialty of thoracic surgery consists of the diagnosis and

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[†] Modified from "Guidelines for Hospital Privileges for Thoracic Surgeons," developed by The Society of Thoracic Surgeons, endorsed by The American Association for Thoracic Surgery in 1986, and revised in 1991 and 1992. Copies may be obtained from: The American Association for Thoracic Surgery, Thirteen Elm St, Manchester, MA 01944; or The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611-4267.

treatment of the major organs comprising the thorax, but is not totally confined to this area. More precisely, it includes the surgical treatment of congenital anomalies, malfunctions, diseases, and injuries of the thoracic cage, the heart and great vessels, the tracheobronchial system and lungs, esophagus, diaphragm, other mediastinal contents, and circulatory systems in all age groups.

This specialty is recognized by certification by the American Board of Thoracic Surgery or fellowship in cardiovascular and thoracic surgery in the Royal College of Surgeons of Canada, or certification of special competence in general thoracic surgery by the Royal College of Surgeons of Canada. Certification requires specific training in an approved residency program which educates its students in both the diagnosis and treatment of diseases, malfunctions, and injuries of the thoracic cavity and its contents. This requires a detailed knowledge of normal and abnormal anatomy and physiology within the cardiorespiratory and gastrointestinal systems. Specific technical and cognitive skills must be learned both in the operating theater and in the post surgical setting which allow for excision, repair or replacement (via tissue transplant or prosthesis) of the contents of the thorax. These abilities must include detailed knowledge of and expertise with the operative techniques, the medications, and technological hardware required for the safe and expeditious performance of these procedures.

Fields of expertise practiced by thoracic surgeons include: 1) Benign and malignant tumors of the lung, chest wall, esophagus and stomach and mediastinal contents; 2) Coronary artery disease and its complications; 3) Diseases of the great vessels; 4) Valvular heart disease; 5) Electrophysiological arrhythmia ablation and pacemakers; 6) hernias and other pathology of the diaphragm; 7) Malfunctions of the esophagus; 8) Congenital and developmental anomalies of the cardiovascular system, diaphragm, esophagus, trachea and all structures within the chest; 9) Gastrointestinal endoscopy; 10) Bronchoscopy, thoracoscopy, and mediastinoscopy; 11) Peripheral vascular surgery as associated with major vessel disease; and 12) Blunt and sharp injuries to the thorax (trauma) including preoperative diagnosis, surgical evaluation, operative management and postoperative care.

An appropriately trained and credentialed thoracic surgeon should be expected to request privileges in those areas covered by his training. Training in Canadian programs is not in every case equivalent to that required by the ABTS. In those instances, the actual training received must be evaluated in the process of granting privileges. Those privileges may include, but not be limited to, the following list:

Thoracic and cardiovascular surgical privileges (for adults and children)
All operations involving resection, reconstruction, repair or biopsy of the lung and its parts (e.g. pneumonectomy, lobectomy, segmentectomy, localized resection, sleeve resection, in continuity with chest wall resection, including transplantation, etc., but not limited to these); and procedures incidental to the above.
All operations involving resection of the chest wall or the pleura, such as resection of chest wall tumor, pleurectomy, decortication, thoracoplasty, resection of first (or other) rib(s), empyema drainage, sternoplasty (for pectus excavatum or carinatum), etc., but not limited to these; and procedures incidental thereto.
All operations involving resection, reconstruction or repair of the trachea and bronchi, such as tracheostomy, tracheal resection, bronchotomy, bronchoplasty, etc., but not limited to these; and procedures incidental thereto.
All operations involving resection, reconstruction or repair of the esophagus and diaphragm, such as diverticulectomy, esophagectomy, esophagogastrectomy, colon interposition, jejunal interposition, hiatal herniorrhaphy, removal of diaphragmatic tumors, repair of the diaphragm, etc., but not limited to these; and procedures incidental thereto.
All operations of the pericardium, involving resection, reconstruction, drainage, etc., such as pericardiectomy or pericardiotomy, but not limited to these; and procedures incidental thereto.
All endoscopic procedures and instrumentations involving the esophagus and tracheobronchial tree, such as laryngoscopy, bronchoscopy, thoracoscopy, esophagoscopy, esophageal dilatation, etc., but not limited to these; and procedures incidental thereto.
Lymph node and superficial biopsy procedures, such as scalene or axillary node biopsy, subcutaneous and muscular biopsy etc., and procedures incidental thereto.
All procedures involving biopsy, excision of tumor, drainage, etc., of the mediastinum, such as mediastinoscopy or mediastinotomy, but not limited to these; and procedures incidental thereto.
Closed heart operations, both congenital and acquired (including reconstruction with grafts)
Open heart operations, both congenital and acquired (including valvuloplasty, replacement, reconstruction with grafts or transplantation)
Surgery of tumors of the heart and pericardium
Surgery of arrhythmias (arrhythmias ablation)
Surgery for implantation of artificial heart and mechanical devices to support or replace the heart partially or totally.
Correction or repair of all anomalies or injuries of great vessels and branches thereof, including aorta, pulmonary artery, pulmonary veins, venae cavae, but not limited to these; and procedures incidental thereto.
All operations for myocardial revascularization (endarterectomy, bypass grafts or internal mammary artery or other grafts to coronary arteries).
Operative procedures for correction or palliation of arteriosclerotic vessels, including the aorto-iliac-femoral system, but not limited to these; and procedures incidental thereto.
All operations for placement or replacement of cardiac pacemaker systems, including multi-chamber sensory pacemakers, automatic implantable defibrillators, whether epicardial or pervenous approach, but not limited to these; and procedures incidental thereto.
All operations involving transplantation of the heart, heart-lung block, and single or double lung transplants.

These guidelines have been developed by the Ad Hoc Committee for Cardiothoracic Surgical Practice Guidelines of The Society of Thoracic Surgeons. Numerous professional organizations have been involved in the development of the practice guidelines, and there is a diversity of opinion concerning their format and content. Because there are no established standards for writing practice guidelines, they have tended to vary from organization to

organization according to the perceived needs of the particular specialty.

The Society of Thoracic Surgeons has elected to develop guidelines that are brief, broadly interpretable, helpful to practicing clinical cardiothoracic surgeons, and useful to those assessing quality of cardiothoracic surgical care. After considerable deliberation and discussion, the guideline format developed by the American College of Obstetricians and Gynecologists‡ was modified to fulfill the needs of practicing cardiothoracic surgeons and their patients. The guidelines were then developed and modified during an arduous review process. The general outline includes the following: Diagnosis, Procedure, Indication, Confirmation of Indication, Relative Contraindications, Actions Prior to Procedure, Actions During Procedure, Actions Following Procedure, Outcome and References. To make these guidelines relevant to cardiothoracic surgical practice, coding diagnoses with their codes and the procedure codes are indicated in each guideline. Lack of appropriate codes for newer procedures made coding difficult, if not impossible, in some instances.

From the inception of this task, it was acknowledged that practice guidelines could not and should not be all-inclusive. The development and application of guidelines must remain a dynamic process. Principles considered essential or important in a guideline at one time might become irrelevant or inappropriate at a later time. Extensively detailed and documented guidelines for the entire field of cardiothoracic surgery would approach the size of a textbook of cardiothoracic surgery, and would be obsolete before they were published.

Cardiothoracic surgical textbooks are updated frequently. Many of the Committee members have been contributors to these texts. Their selection as textbook contributors and Committee members acknowledges their clinical expertise in the field of cardiothoracic surgery. These guidelines have been developed by subcommittees of selected experts and educators, knowledgeable in the field of cardiothoracic surgery and especially the specific area to which they were assigned. Their curricula vitae will be available for review at the business office of The Society of Thoracic Surgeons.

As an initial entry into the field of practice guideline development, subcommittees in each of nine areas of the field of cardiothoracic surgery were charged with developing guidelines for three of the more commonly performed procedures in their designated area. These areas are: ischemic heart disease; valvular heart disease; thoracic aortic disease; transplantation and assist devices; arrythmias; bronchopulmonary disease; chest wall, diaphragmatic, mediastinal, and pericardial disorders; congenital heart disease, and esophageal disease.

After thorough deliberation, it was decided to have these guidelines procedure oriented. The thrust for development of these guidelines was to assure the opportunity for the best and most complete cardiothoracic surgical care for each patient. Issues of appropriateness and quality must be defined before cost can be assessed. The Committee is aware of its responsibility to each patient and to society to deliver this care in the most cost-efficient manner.

General recommendations that are applicable to the delivery of care to all cardiothoracic patients are presented separately. Basic preoperative evaluation and the necessary supporting services are identified in the following sections.

The Preoperative Evaluation

To be certain that the contemplated operation will not propose an undue risk to the patients, those who are candidates for a major thoracic or cardiac procedure should undergo a thorough preoperative evaluation. This evaluation is designed to detect concomitant medical diseases that might prove to contraindicate operation or that may require further treatment in preparation for the proposed surgical procedure. The following represents the minimum required preoperative evaluation and should be performed within one week of the date of operation.

1. Thorough history and physical examination
2. Chest roentgenogram
3. Urinalysis
4. Electrocardiogram
5. Blood sample for typing in all patients and a type and crossmatch for blood products in cases having a risk of significant blood loss. Patients who have previously provided blood via autologous donation may be excused from this requirement.
6. Blood analysis to include complete blood count, platelet count, PT, PTT and SMA-18.
7. Room air blood gas determination including pCO_2, pO_2, and pH in patients with suspected pulmonary compromise.
8. Appropriate medical consultation where indicated.
9. Assessment of nutritional status.

Institutional Requirements

There are certain institutional requirements that must be met if cardiothoracic surgery is to be safely performed within a health care center. These include:

1. Blood Bank—The performance of cardiac surgery necessitates an active and competently managed blood bank. At times, a blood bank may be called upon to provide large quantities of many different types of blood components with little or no notice. The presence of such a facility within the hospital is mandatory if major cardiothoracic surgery is to be performed safely.
2. Intensive Care Units—Adequate postoperative care often mandates complex equipment for treatment and the monitoring of many hemodynamic indices and

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‡ Quality Assurance in Obstetrics and Gynecology, 1988 Edition, The American College of Obstetricians and Gynecologists, 409 12th St SW, Washington, DC 20024-2188.

other clinical parameters simultaneously. A hospital should have both the equipment for and medical, nursing, and ancillary personnel experienced in postsurgical critical care delivery if patient needs are to be met satisfactorily. Due to the needs for emergency intervention which occasionally arise in the postoperative period, there should be a physician on call within the hospital, preferably one with experience in the care of critically ill patients.

3. Anesthesiology—The safe performance of cardiothoracic surgical procedures requires a cooperative effort between surgeon and anesthesiologist. The critical nature of these patients and the multiple cardiopulmonary manipulations that inevitably occur require anesthesiologists who are expert in the delivery of care to patients with complex cardiac and thoracic problems. These anesthesiologists must be familiar with all types of ventilators, monitoring equipment, and other supportive equipment. Anesthesiologists with special interest in cardiothoracic surgical problems are preferable.
4. Operating Rooms—Both postoperative complications and primary cardiothoracic emergencies frequently require urgent operative intervention. An institution must therefore have the capability to rapidly mobilize surgical and support teams for emergency procedures 24 hours a day, seven days a week.
5. Medical Consultation Services—Supportive expertise must be available 24 hours a day, seven days a week in medical subspecialty fields such as cardiology, pulmonology, neurology, hematology, nephrology, and infectious disease.
6. Respiratory Therapy—The modern delivery of critical care requires around the clock availability of respiratory care personnel familiar with the operation, function, and maintenance of a wide variety of modern life support equipment.
7. Radiology—Around the clock radiologic services must be available in the fields of diagnostic radiology and nuclear medicine.
8. Laboratory and Pathology Services—Around the clock laboratory services must be available for immediate blood gas analysis and determination of serum biochemical and hematologic including coagulation values.

Practice Guidelines

Chest Wall, Diaphragm, Mediastinum, Pericardium: I

Diagnosis:	353.0	Brachial plexus lesions
	756.2	Cervical rib
Procedure:	21615	Excision first and/or cervical rib for outlet compression syndrome
Indication:	1)	Pain refractory to intensive physical therapy rehabilitation program
	2)	Neurologic impairment consistent with thoracic outlet syndrome (TOS)
	3)	Compression of subclavian artery and/or vein
Confirmation of Indication:	1)	Chest radiograph
	2)	Consultation with neurologist or neurosurgeon
	3)	Radiograph, magnetic resonance imaging (MRI) and/or computed tomography (CT) of cervical spine
	4)	Nerve conduction studies and electromyogram (EMG)
	5)	Angiography if indicated
	6)	Arm phlebography if indicated
Relative Contraindications:	Lack of objective evidence for compression syndrome	
Actions Prior to Procedure:	1)	Intensive trial of physical therapy
	2)	Consultation with neurologist or neurosurgeon
	3)	Radiograph, MRI, and/or CT of cervical spine
	4)	Nerve conduction studies and EMG
	5)	Psychological evaluation if indicated
Actions During Procedure:	Relief of compression syndrome (operative approach optional and dependent upon objective findings)	
Actions Following Procedure:	1)	Monitor for pneumothorax
	2)	Monitor neurologic and vascular status of involved extremity
Outcome:	1)	Mortality less than 1%
	2)	Discharge 7 days or less
	3)	Relief of compression syndrome symptoms

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Practice Guidelines

Chest Wall, Diaphragm, Mediastinum, Pericardium: II

Diagnosis:	162.9	Malignant neoplasm of bronchus and lung, unspecified
	165.8	Malignant neoplasm of respiratory and intrathoracic organs
	165.9	Malignant neoplasm of ill-defined sites within the respiratory system
Procedure:	39400	Mediastinoscopy
Indication:	Primary carcinoma of lung	
Confirmation of Indication:	Radiographic or histologic evidence for lung cancer	
Relative Contraindications:	1)	Previously established diagnosis of metastatic small cell lung cancer
	2)	Presence of disseminated disease
	3)	Permanent tracheostomy
Actions Prior to Procedure:	1)	Rule out disseminated disease
	2)	Rule out supraclavicular adenopathy by physical examination
Actions During Procedure:	1)	Biopsy of suspicious lymph nodes or masses on ipsilateral and contralateral side
	2)	Frozen section evaluation of tissue to assure adequacy of diagnostic material, if indicated
Actions Following Procedure:	1)	Observe for bleeding and/or respiratory difficulty
	2)	Chest radiograph if indicated
Outcome:	1)	Mortality less than 1%
	2)	Obtain diagnostic tissue or document lack thereof
	3)	Discharge less than 48 hours

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Practice Guidelines

Chest Wall, Diaphragm, Mediastinum, Pericardium: III

Diagnosis: 530.1 Esophagitis
552.3 Diaphragmatic hernia with obstruction
552.9 Hernia of unspecified site with obstruction
553.3 Diaphragmatic hernia
553.9 Hernia of unspecified site

Procedure: 39520 Repair, diaphragmatic hernia (esophageal hiatal); transthoracic

Indication: Reflux esophagitis

Confirmation of Indication: One or both of the following in a patient with intractable symptoms:

a. Biopsy proven esophagitis
b. Prolonged (≥8 h) esophageal pH testing

Relative Contraindications: Inadequate pulmonary reserve

Actions Prior to Procedure:

1) Barium swallow
2) Upper gastrointestinal endoscopy
3) Prolonged (≥8 h) esophageal pH testing
4) Evaluation of pulmonary status

Actions During Procedure: Anatomic restoration of gastroesophageal (GE) junction, including:

a. Fundoplication
b. Crural repair

Actions Following Procedure:

1) Monitor nasogastric drainage
2) Barium study within 2 weeks

Outcome:

1) Operative mortality less than 1%
2) Relief of symptoms
3) Discharge in 7–10 days

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CORRESPONDENCE

Extracorporeal Membrane Oxygenation Revisited, Revisited

To the Editor:

In an editorial referring to our report on extracorporeal life support in adult respiratory failure (ARF), Bosken and Lenfant [1] point out that many things have changed in the 18 years since the NHLBI-sponsored adult extracorporeal membrane oxygenation (ECMO) study was designed. We agree; this is why we conducted the phase I—safety and efficacy—"ECMO Revisited" clinical experience reported in this issue of *The Annals* [2]. Bosken and Lenfant comment that research on extracorporeal life support (ECLS) should be based on carefully designed protocols incorporating modern understanding of pulmonary pathophysiology, supportive treatment, and ECLS technology. They argue that reference to the 1974 to 1979 NHLBI ECMO study [3] is outdated, and the current mortality risk of the 1973 selection criteria is unknown. We agree, and included this discussion in our manuscript. However we welcome the opportunity to provide further commentary.

See also pages 551 and 553.

How should a new high-technology treatment proceed from laboratory to clinical study to clinical practice? This was the topic of an NIH workshop conducted in June 1990 using the diffusion of ECMO for neonatal respiratory failure as an example [4]. Neonatal ECMO began with laboratory development and depends on continuous refinement through basic research. Phase I clinical trials in moribund infants were conducted until (1) the technique was stable and standardized, (2) relative risk and safety were documented, and (3) results allowed formulation of a hypothesis for a phase II evaluation. Two prospective, randomized (phase II) trials were done in centers with preliminary experience in more than 50 cases. A phase III prospective, randomized trial demonstrated improved cost-effectiveness compared with other contemporary therapy. This research on neonatal ECMO has been sponsored by the NIH since 1972. A record of all cases (now more than 6,000) is maintained in a central Registry, documenting patient characteristics, risk and safety, and growth of the technology as clinical research became clinical practice. Our research group was responsible for much of the neonatal ECMO research, and we are following the same sequence in the reevaluation of ECLS in adult and pediatric respiratory failure.

We participated in the 1974 to 1979 NHLBI adult ECMO study design and implementation. That was a benchmark project because it was the first prospective, randomized study of a life support technique in which the end point was death. There were many problems with the study [5], but we learned many lessons: Characterize the patient population and results of standard treatment first. Conduct the study only in centers that are very experienced with both standard and experimental treatment. Use a randomization design that minimizes the logistical and ethical dilemmas. Assure enough diversity of patients that the study will not be dominated by a single patient group. Stop the study when one treatment is clearly better, or when there is clearly no difference. All of these concepts were applied to the development of neonatal ECMO including the design of the prospective, randomized studies of life support.

It was appropriate to stop the 1974 to 1979 study prematurely, and the results and conclusions were accurate and appropriate. Why, then, are we revisiting adult ECMO now? For all the reasons that Bosken and Lenfant enumerate, and more. Modern understanding of lung injury, recovery, and supportive treatment has definitely improved both prevention and outcome in severe respiratory failure. We have learned to avoid or treat overhydration, systemic sepsis, oral-gastrointestinal contamination, anemia, supine positioning, oxygen toxicity, and barotrauma. But mortality persists, and the patient who gets to the stage of 100% oxygen and high airway pressure *despite and after* our best efforts is sicker now than the same patient in 1973. From Gattinoni and Kolobow [5] we learned that the ventilator management in ECMO-treated patients in the NHLBI study was all wrong. Why go to all the trouble and risk of extracorporeal support, then leave the patient at high O_2 and airway pressure? The same investigators suggest that the use of venoarterial (rather than venovenous) bypass might have contributed to lung injury. They reported 50% survival, and others have corroborated their report. From the experience with ECMO in newborn infants and children we learned that survival is more than 90% in patients with reversible disease, that bleeding should be a rare complication, that devices for ECLS are safe and reliable during weeks of continuous use, and that successful management of ECLS requires a large and well-trained team. There was reason to believe that ECLS should be revisited. Bosken and Lenfant agree that reevaluation of adult ECLS is appropriate. *The questions are: how to select moribund but salvageable patients for phase I studies, and when to design and fund phase II prospective, randomized trials?*

The answer to the first question is realistically simple. No matter what physiologic criteria are used—even with correlative mortality data from that institution or from the literature—the skeptical reader will argue that the patient might have survived with better conventional therapy (preferably in his or her own institution). The 1974 NHLBI ECMO entry criterion is as good or as bad as any, and it has been used (and reverified) consistently over many years. When the parameters are measured after and despite all appropriate treatment, patients with high mortality risk are identified. That is the only purpose of selection criteria for a phase I study, and as long as the preintervention treatment and patient characteristics are described, anyone can repeat the study. We reported that 4 patients who met our entry criteria but were not treated with ECLS all died, but the skeptical reader would appropriately argue that our care was inadequate. We can only ask the reader to trust that our conventional management of adult respiratory failure is as good as his or hers.

The second question is more challenging, and we addressed it in our discussion. Another prospective, randomized study of adult ECLS should be done when both ECLS and conventional treatment are standardized and characterized; in a center or centers with experience with 50 ECLS patients; when mortality and morbidity risk with standard treatment is well characterized; and when an adequate diversity of salvageable patients can be assured.

In the meantime, based on reported experience with more than 400 patients in the modern era, we know that the survival of adult respiratory failure treated with ECLS is at least 50%. This is better than the results of any other treatment with a survival of, say, 20%. This experience is corroborated in our own phase I trial reported in this issue. Therefore we describe ECLS as extraordinary but appropriate (not experimental) treatment for patients with reversible respiratory failure when the treating physician believes (based on the best measurements available) that the chance of survival is less than 20%.

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Esophagogastrectomy for Acid Injury

To the Editor:

In their article on emergency esophagogastrectomy for corrosive injury, Horváth and collaborators [1] wrote that damage to the stomach is generally observed in the antrum and fundus, but acute necrosis usually affects the major part of the stomach and is only very rarely cured by partial resection. This has been our experience, too. They added that they always perform total esophagogastrectomy and the esophagus is resected without a thoracotomy. We behave differently concerning the esophagus [2].

In a group of 80 patients treated for severe corrosive esophagogastric burns, total gastrectomy had to be performed in 20 patients because of necrosis and perforation. It was done within 24 hours in 12 patients: 5 had ingested an acid (2 >150 mL, 2 <150 mL, 1 unknown quantity), 4 had ingested a base (1 >150 mL, 1 <150 mL, 2 unknown quantities), 2 had ingested bleach (>150 mL), and 1 had ingested formaldehyde (<150 mL). Gastrectomy was done between postinjury days 1 and 20 in 8 patients: 1 had ingested an acid (<150 mL), 3 had ingested a base (2 >150 mL, 1 unknown quantity), and 4 had ingested bleach (>150 mL). The duodenum, cardia, and cervicothoracic esophagus were hand-sutured. A terminal cervical esophagostomy and a feeding jejunostomy were performed.

Five of the 20 patients died in the postoperative period: of multiple small bowel perforation on day 9, of peritonitis on day 18, of systemic sepsis on days 2 and 18, and of a tracheoesophageal fistula on day 33. The 15 survivors had a second-stage retrosternal colon interposition bypassing the excluded esophagus. One died of complications of an esophageal mucocele at 4 years, 4 were found to have a nonsymptomatic small esophageal mucocele, and 1 had a regressive mucocele.

When necrosis from ingestion of caustic material is present in the abdomen, aggressive operation is often necessary [3]. If the burns extend to the bowel and pancreas, extended resections with delayed sutures and with enterostomies offer the only chance of cure. What is to be done with the esophagus is more debatable: esophagojejunal anastomosis may be attempted in a small minority of well-selected cases, the esophagus can be sutured over a drain, it can be closed at both ends and excluded, or it can be resected.

Blind resection is easy but may be unnecessary, and it may provoke a tear in the membranous part of the trachea. It has been advocated to stop extensive necrosis of the esophagus from reaching the trachea. However its mortality is high [4, 5]. Those who resect the esophagus as a preventive measure also state that if endoscopy discloses necrosis of the trachea, one should refrain from performing an esophagectomy.

In our series, all the patients who died had an autopsy. The esophagus was not the cause of death except in the case of the patient with a tracheoesophageal fistula that appeared on day 33: this was the only failure of exclusion. Two patients underwent emergency bronchoscopy because of respiratory disorders associated with stage III esophageal burns: 1 of them had a white area on the posterior surface of the trachea and left bronchus, and 1 had no lesion. They both recovered. The excluded esophagus did not invite immediate danger in our experience, but it could produce a secondary mucocele (which was retrospective proof it was not very deeply burned, as endoscopy generally overestimates the lesions). So we suggest immediate exclusion of the esophagus in the majority of cases to avoid the supplementary trauma of resection, with subsequent esophagectomy during coloplasty to prevent the formation of a mucocele [6].

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Severe Endobronchial Hemorrhage

To the Editor:

In a recent article, Purut and co-workers [1] described a case of severe endobronchial hemorrhage during a coronary artery bypass operation due to pulmonary artery perforation by a Swan-Ganz catheter. The authors are to be commended for their successful and innovative use of an endobronchial balloon catheter without subsequent pulmonary resection to control the bleeding, but neither their report nor the accompanying discussion commented on the actual need for a Swan-Ganz catheter in their patient. In view of the recognized danger and expense of the Swan-Ganz catheter, it seems pertinent to question its use in a 64-year-old man with no recent infarction and normal cardiac function (ejection fraction 0.67) who was undergoing an operation described as "elective." Unfortunately, Swan-Ganz catheters are often inserted by anesthesiologists without the surgeon's advice or consent, as may have occurred in Purut and co-workers' patient.

It is important to report complications related to Swan-Ganz catheters to document that use of a Swan-Ganz catheter is not innocuous and should not be routine. Information about cardiac output is rarely necessary intraoperatively in low-risk patients after coronary bypass, because such patients should not require inotropic support to be weaned from cardiopulmonary bypass [2, 3]. (A Swan-Ganz catheter can always be inserted postoperatively if circumstances change.) Information about left ventricular filling pressures is useful, however, and can be easily and inexpensively obtained by inserting a left atrial pressure monitoring catheter. For the vast majority of surgeons who vent the heart through the right superior pulmonary vein, the vent site offers a convenient portal for the left atrial catheter.

The recent tendency to use oximetric Swan-Ganz catheters further extends the trend toward technological overkill, because these catheters not only cost considerably more to purchase but provoke more frequent determinations of arterial oxygen saturation and hematocrit, which are usually necessary to assess the significance of any major change in mixed venous oxygen saturation.

The cost of coronary bypass is the focus of increasing scrutiny and is an appropriate concern for surgeons as well as for bureaucrats. The actual cost to use the simplest Swan-Ganz catheter, including the hospital's charge for monitoring and blood gas determinations, the anesthesiologist's charge for insertion of the catheter, and miscellaneous charges for supplies, is a minimum of $300 and exceeds $500 in some cases. Any complication such as the one described by Purut and co-workers raises the monetary cost exponentially and adds a human cost that cannot be quantitated. My colleagues and I therefore attempt to restrict the use of Swan-Ganz catheters for coronary bypass operations to patients with exceptional problems [3]. Although we cannot always achieve this objective, we consider it a worthwhile goal.

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Reply

To the Editor:

Dr Bonchek questions the advisability of routine use of Swan-Ganz catheters during cardiac operations. He is correct in stating that to avoid their use will avoid their associated expense and inherent complications. Nonetheless, it is our practice to use Swan-Ganz catheters in virtually all adult cardiac procedures. We have reached this conclusion based on the documented low risk of serious complications (0.016% for fatal perforation) [1] compared with the benefits provided (direct measure of right-sided pressures, indirect measure of left-sided pressures, cardiac output, and oximetry in selected cases). In no instance is the decision made "without the surgeon's advice or consent."

Dr Bonchek is a skilled surgeon who has been able to simplify his technique in the interest of economy without jeopardizing his patients. It is unlikely, however, that most surgeons when performing coronary artery bypass would elect to avoid the use of protective cardioplegia or physiologic monitoring as proposed by Dr Bonchek [2]. We are not aware of any data to support the contention that left atrial pressure monitoring engenders less risk, is less expensive, or provides equal diagnostic capability when compared with Swan-Ganz catheter monitoring. We are also not aware of data to support the notion that the vast majority of surgeons vent the left heart through the right superior pulmonary vein during coronary bypass operations.

We agree with Dr Bonchek that any complication results in additional monetary and human cost. Complications should be avoided if possible, recognized if present, and treated as effectively as possible. The purpose of our case report was to address these issues.

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"Provocative Clamping" and Removal of Chest Tubes Despite Persistent Air Leak

To the Editor:

The criteria for removal of chest tubes placed at the time of pulmonary resection include (1) complete expansion of remaining lung tissue and (2) cessation of air leakage and fluid drainage. These criteria are usually met within 3 to 5 days after operation.

In a small percentage of patients (around 5%) an air leak persists undiminished well into the second or even third postoperative week and may show no signs of stopping. Such air leaks, which are presumed to come from unsealed raw lung surfaces, are frequently associated with fully or almost fully expanded lung. They are not associated with signs of sepsis or purulent drainage, which might indicate a bronchial stump fistula.

Under these circumstances, after a defective drainage system is ruled out as the source of the "leak" and after a lack of response to manipulations of the degree of suction has been demonstrated, a useful, effective, seemingly unorthodox maneuver is "provocative clamping" of the tubes followed almost immediately by their removal.

The procedure is as follows:

1. The chest tubes are clamped. The patient is observed during quiet breathing and after vigorous coughing for any signs or symptoms of tension pneumothorax.
2. If clamping of the tubes is well tolerated clinically, a chest roentgenogram is taken during inspiration and expiration.
3. If there is little or no change in the degree of pulmonary expansion or the size, of the pneumothorax (if present), the tubes are unclamped. Vigorous coughing is again encouraged, noting whether or not an excessive gush of air comes through the tubes.
4. The same sequence of roentgenograms is repeated with the tubes unclamped.
5. If little or no change is noted, the tubes can be removed with safety. The patient may then be discharged in a day or so. A small to moderate residual pneumothorax will be absorbed spontaneously within a week or two.
6. The procedure should be discontinued at any point if untoward symptoms appear.

This program is useful in successfully terminating indefinite tube drainage and air leakage, and in avoiding any further prolongation of hospital stay. The patient is discharged with an intact chest and no tubes.

The problem of prolonged postoperative air leak has been addressed by Adkins and Aaron [1], Brooks [2], and Kirsh and associates [3], and at greater length by Piccone and Faber [4]. The latter present an algorithm for persistent leaks over 7 days. None of these authors advised "provocative clamping." Other recommendations include artificial pneumoperitoneum, removal and replacement of tubes, Heimlich valve to maintain drainage while ambulatory, chemical pleurodesis, reoperation and closure of air leaks, pleural "tent," phrenic nerve crush, and relocation or transplantation of the diaphragm.

"Provocative clamping" is simple, safe, and effective. It should be almost unheard of to have to resort to any of these other procedures except in the rarest of circumstances.

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Thoracoscopy and Talc Poudrage

To the Editor:

I greatly appreciated the report on the use of talc and thoracoscopy in pleural effusion and pneumothorax [1]. The decision to employ talc rather than other scarifying agents is backed up by anyone who has reported on series comparing talc with other agents. I have been using talc for about 40 years [2] in patients, much as those described, for a variety of benign and malignant effusions and a variety of types of pneumothorax, including in postoperative patients, with excellent results. For example, I have come to use talc in initial spontaneous pneumothorax of such a degree that intubation is deemed necessary and have not done an open thoracotomy in more than 15 years for either recurrent or primary spontaneous pneumothorax. In pleural effusions or pneumothorax I have not used thoracoscopy and have employed instead a suspension of 5 to 15 g of talc instilled usually through two No. 36 Argyle-type catheters in the midaxillary line, one inserted in the posterior gutter and the other anteriorly. These tubes are clamped after talc suspension instillation, and the patient is positioned head down and then the reverse to distribute this suspension over the pleural and lung surfaces. The effusions are usually at least partially drained before talc instillation. This procedure I do in the operating room so that an epidural catheter for analgesia can be inserted for a few days, but only a nerve block anesthesia is employed. Twenty to 60 cm H_2O suction is usually immediately and continuously applied after return to the ward for as many days as necessary for the lung to expand and drainage to become minimal. I have found that a coagulum forms where residual space without lung leak is present, and one may get a good result even if incomplete lung expansion because of peel (thickened parietal pleura) is present. Occasionally I have had to use a third or even a fourth tube anteriorly or wherever a pocket persists. I have not had to operate on any chylothorax patients, avoiding major operations by using this technique. I have also tried this technique on all manner of effusions, mostly neoplastic, however.

The epidural catheter for analgesia [3] over several days has allowed chest wall motion to be enhanced from the time of the talc instillation (for cough promotion and physical therapy). The use of high suction when necessary has assisted in leak sealing. Occasionally, extra talc has been instilled through the tubes when a lung leak persists, particularly after a resective operation. The talc suspension is bottled by the pharmacy under sterile conditions and is available throughout the hospital. I would like to ask that this technique be tried in lieu of thoracoscopy, which, many have complained, is cumbersome and unnecessary. I believe that the excellent results shown in this report can be duplicated with the use of a talc suspension and intercostal intubation *alone.*

John S. Chambers, MD

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References

1. Daniel TM, Tribble CG, Rodgers BM. Thoracoscopy and talc poudrage for pneumothoraces and effusions. Ann Thorac Surg 1990;50:186–9.
2. Chambers JS. Palliative treatment of neoplastic pleural effusion with intercostal intubation and talc instillation. West J Surg Obstet Gynecol 1958;66:26–8
3. Mehnert JH, Dupont TJ, Rose DH. Intermittent epidural morphine instillation for control of postoperative pain. Am J Surg 1983;146:145–51.

Reply

To the Editor:

Dr Chambers supports our experience regarding the effectiveness of intrapleural talc for the treatment of selected pneumothoraces and effusions. We believe in most cases of effusion the use of his technique in place of thoracoscopy and general anesthesia would be quite effective. His technique, however, does describe the use of the operating theater with a thoracic epidural catheter and subsequent rib blocks. In our hands we believe that once the patient is already in the operating theater, general anesthesia is more comfortable for patients who are often dyspneic and fearful of further pain. We would strongly agree with his statement that it is important to confirm that the lung has not been trapped and that the pleural surfaces can be apposed after draining the fluid from the chest. We accomplished this principle by visualizing the pleural surfaces under thoracoscopy with the lung inflated. The use of thoracoscopy allows, in addition, visualization and lysis of scattered adhesions that might otherwise impair complete pleural covering with talc. Our article did report from the literature 2 cases of respiratory distress syndrome associated with the use of talc in a saline suspension. We have not observed this phenomenon with the thoracoscopic delivery of talc but have no reason to think that delivery by saline suspension necessarily caused the described complication.

In summary, we believe we both agree over the effectiveness of intrapleural talc, and whether this is accomplished in an aerosolized form or in a saline suspension—as recommended by Dr Chambers—remains a matter of choice.

Thomas M. Daniel, MD
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Bradley Rodgers, MD

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Pacemaker Lateral Approach

To the Editor:

I read with interest the recent article by Dr J. Ernesto Molina [1]. Dr Molina's description of a lateral approach for implanting pacemaker generators in the chest wall of women and children is appreciated. Experience with a recent patient leads me to offer one note of caution.

In February 1990 a 30-year-old woman was seen at our institution after having had a pacemaker inserted 4 months previously at another institution for problems associated with the Wolff-Parkinson-White syndrome. The pacemaker pocket had been placed somewhat lateral and deep to the breast through an incision similar to that described by Dr Molina. However, this particular patient's incision extended into the apocrine sweat gland-bearing area of the axilla. The patient had a painful pacemaker pocket that was initially believed to be due to its location—too close to the axilla. At the time of operation, cultures were obtained that revealed a low-grade bacterial infection with a coagulase-negative staphylococcus. The patient subsequently underwent complete removal and replacement of the pacemaking apparatus at a distant site at a separate surgical sitting.

The cosmetic placement of pacemaker generators is a desired goal. I think that the incisions for these should not be into the apocrine sweat gland areas of the axilla, as these glands are more likely to have a greater bacterial content and may lead to a higher prosthetic infection rate.

Michael K. Wood, MD

1828 El Camino Real, Suite 802
Burlingame, CA 94010

Reference

1. Molina JE. New technique for pacemaker implantation in the upper chest of children and women. Ann Thorac Surg 1991; 51:992–5.

Reply

To the Editor:

As Dr Wood says in his letter, the pacemaker location was "too close to the axilla." This is a common mistake in using this approach when the pocket is not made in the proper location.

As I indicated in my publication (under operative technique), the center of the pocket should lay 5 cm from the midline anteriorly and 10 cm down from the clavicle in adult patients. Figure 1 shows, with the forceps, the area where the pulse generator should be located. When properly done, it never even reaches the lateral border of the pectoralis major muscle.

Therefore, in that particular patient of Dr Wood's, the pocket was not in the proper place from the beginning, as he states. I would like to also point out that if the incision is carried up toward the axilla, it should never pass the hairline as is indicated in Figures 1 and 2. The incision curves posteriorly when reaching the proximity of the hairline of the axilla.

In this manner, the surgeon will never enter the apocrine sweat gland area under any circumstances. It looks like the technique used in the patient that Dr Wood mentions was not the one I described in my publication.

Because I do not know all the details of this particular case described by Dr Wood, I would like to mention that all these patients preoperatively are given cefamandole intravenously to prevent any possible infection by staphylococcal organisms, particularly methicillin-resistant strains.

In our experience, we have not had any infections of pacemaker systems using the lateral approach.

J. Ernesto Molina, MD

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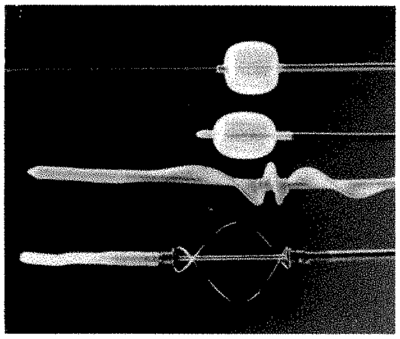

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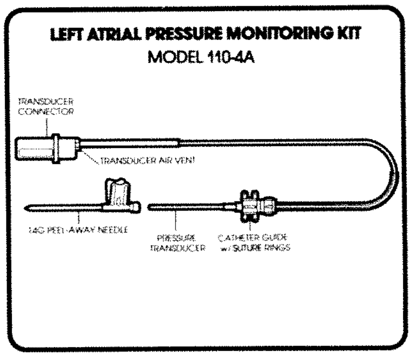

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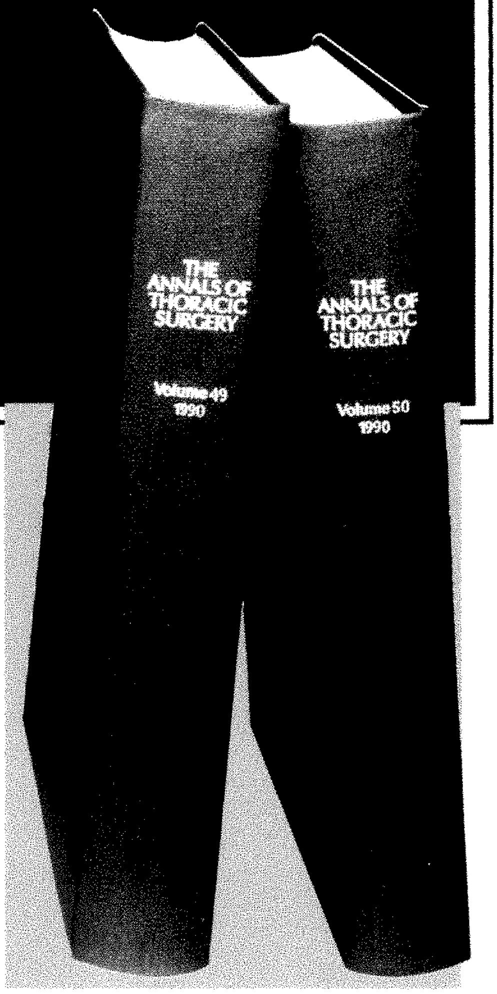
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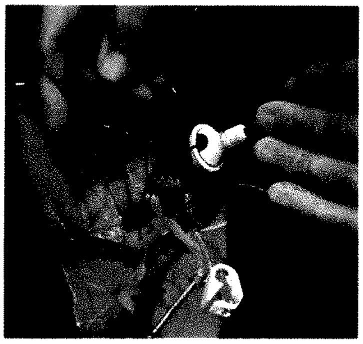

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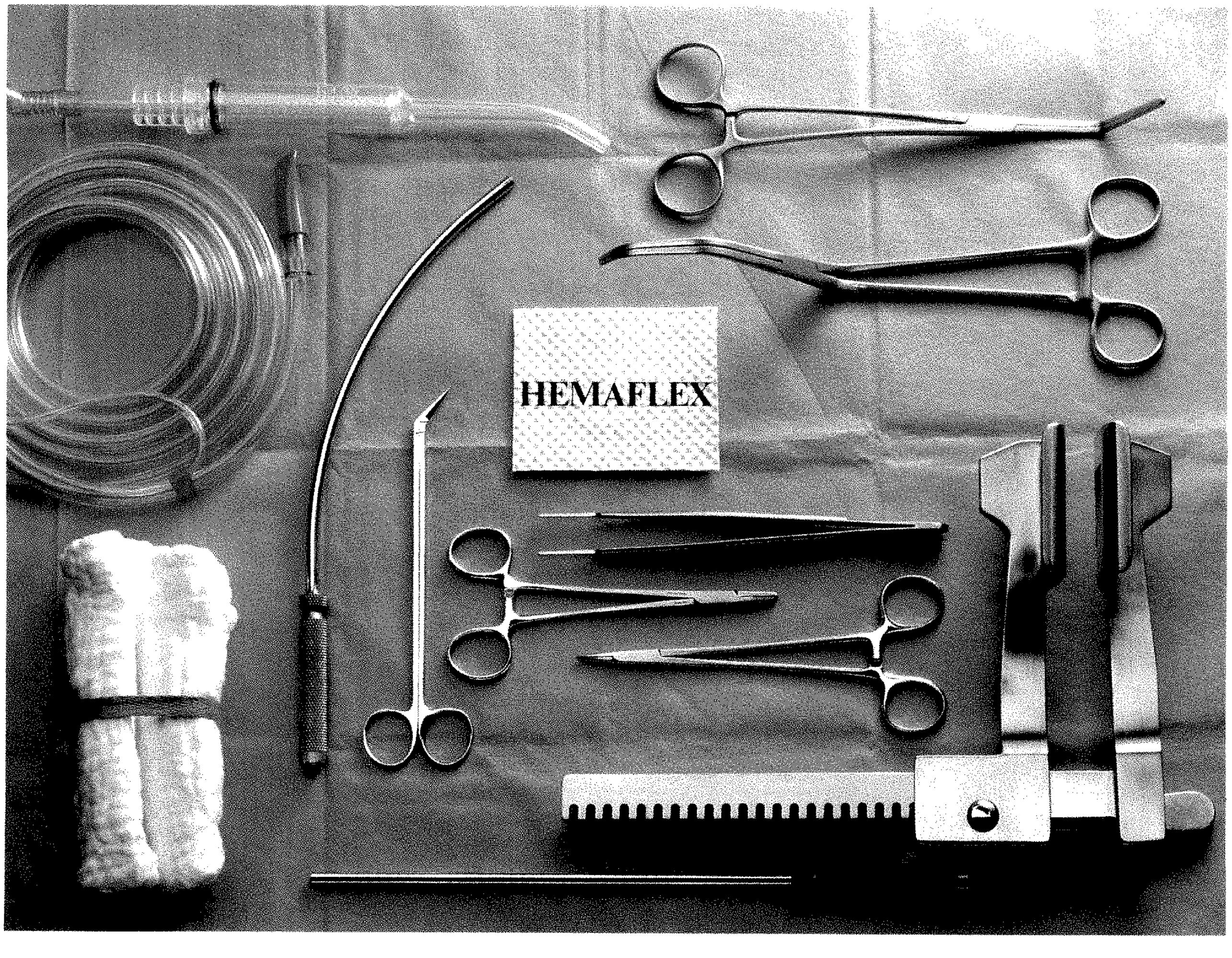

If Not the Art, Why the Science?

Robert W. Jamplis, MD

Palo Alto Medical Foundation, Palo Alto, California

To be elected to the presidency of this august society fills one with pride and humility, and is an honor that I shall cherish the rest of my life. I would like to divide my remarks this morning into three parts—first I will talk a bit about The Society itself, why it was founded and what it does. Second, I will say something about the health care climate in which we find ourselves today and to which we must adapt; I will also look into my crystal ball and predict some possible future scenarios. Finally, and most important, I will cover what the young cardiothoracic surgeon must do (and I am talking today mainly to the back of the room) to command the respect and love of his or her patients, and to restore the lost noble image of all physicians, which is our proud heritage.

Although our history is short, The Society has evolved into one of the premier specialty organizations in the country. Its founders were truly among the giants of thoracic surgery, and in the early 1960s they recognized the need for another thoracic surgical organization other than the American Association for Thoracic Surgery, whose membership was limited to 350. There were then more than 1,000 diplomates of the Board of Thoracic Surgery, and so in St. Louis in January 1965 The Society held its first meeting. Simultaneously volume 1, number 1 of *The Annals of Thoracic Surgery* was published, and as they say, the rest is history.

There were many who were responsible for the organization of The Society but none more instrumental than the great Max Chamberlain (Fig 1). He was joined by Adam Cowley, Ralph Alley, Don Effler, Lyman Brewer, Don Paulson (Fig 2), and others, and Paul Samson was elected the first president (Fig 3). His vice-president was Tom Burford, the treasurer Bob Ellison, and the secretary Frank Byron. The first editor of *The Annals* was John Steele (Fig 4), to be ably succeeded by Herb Sloan and now Tom Ferguson.

They all realized the need for another forum and another journal for all thoracic surgeons, and The Society now has more than 3,000 members both national and international. What they did not visualize, and why I am mentioning something of The Society in this address, is the amazing number of activities this Society undertakes on behalf of cardiothoracic surgeons throughout the country. The scientific meetings and *The Annals* are, of course, of paramount importance. But the number of services and committees is truly extraordinary. I have been impressed with the leadership of the Council and committee members who, when problems have arisen, could have followed the same advice that, according to Winston Churchill, Victorian mothers gave their daughters on their wedding night, namely, "Lie still, and think of England." Instead they have tackled them with skill, intelligence, and hard work, and rather than seeing roaring lions in the road they have preferred to see dead lions in the ditches—which is a true test of leadership.

Our activities in Washington, DC, have been numerous with the Resource-Based Relative Value Study heading the list. With the Abt Associates study we accurately and logically presented our case to the Physician Payment Review Commission and the Health Care Financing Agency. And although we may have lost round one we have reason to believe there are nine to go, and we plan to be in at the finish.

Of equal importance will be how we fare in obtaining correct CPT-4 codes for all of the procedures we do in cardiothoracic surgery, and we are working hard on these.

Our database for cardiac procedures continues to grow, and hopefully we will start the data collection for general thoracic procedures soon. Until we have all the data from the databases over several years we will not be able to predict the best and most successful outcomes for various conditions and procedures.

Therefore, we will not be able to accurately, and the emphasis is on accurately, write reliable practice guidelines. In the meantime, good but empiric guidelines will be written by us, subject to constant revision as more and more data are obtained. When this is achieved I believe it will be the quality of care that will be enhanced rather

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Presented at the Twenty-eighth Annual Meeting of The Society of Thoracic Surgeons, Orlando, FL, Feb 3–5, 1992.

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Fig 1. Max Chamberlain—prime mover for the new Society.

than just the cost of, or the access to, the care that is delivered, and this is the main feature.

Finally, it is important to note that the STS and the AATS were never meant to be, nor are they, in competition with each other. Rather they were meant to be, and are, complementary to each other. To attest to this fact are the number of joint committees of the two organizations, many formed this year. The joint committees are the committees on government relations, manpower, social responsibility, nomenclature and coding, and the latest being the thorococopy and video-assisted thoracic surgery and the practice guidelines. And there will be more, I am certain, as time goes by.

I would now like to address some of the critical health care problems looming over this country today. In the 5th century BC on the Greek island of Kos, certain principles concerning the art of medicine were laid down by Hippocrates, and we have followed them more or less for 25 centuries. The science of medicine is a relative newcomer, being about one century old. But it has taken only a few decades of economic chaos to put them and the entire medical profession in jeopardy.

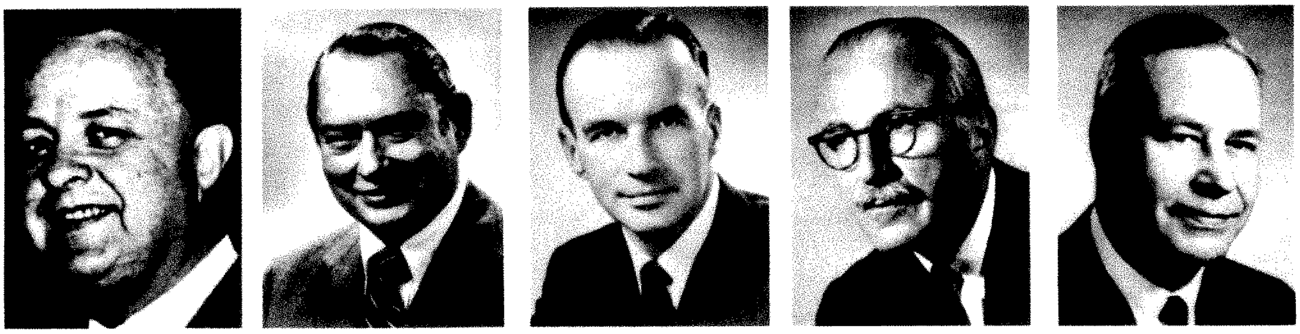
Whether it be among Republicans or Democrats, conservatives or liberals, Congress or the administration, prosperity or recession the debate over the eternal triangle of cost, quality, and access rages. And they are so intrinsically entwined that it is impossible to address one without addressing the other two. Also, it is my firm conviction that cost will be the overriding winner. And thus it will be up to us, the doctors and hospitals, to address the other two issues. Furthermore, because we in the United States have reached a position of such unparalleled preeminence in cardiothoracic surgery, it is our destiny to continue to bring the high standards of care that our patients have come to expect.

However, the most alarming thing is the *rate* at which medical costs have soared. In 1970 they were $75 billion. Twenty-one years later they are $700 billion plus (twice the defense department budget and consuming more than 12% of the gross national product). And by the year 2020, if left unchecked, the whole of the gross national product will go to health care—a totally unrealistic situation.

Thirteen percent of our population or 37 million people are totally uninsured, and 60 million more have inadequate insurance. The reason people are not dying in the streets is because the 200 million people with adequate insurance are unknowingly paying the bill—and this cannot go on forever.

Our aging population and the tremendous technological explosion in science, and particularly in medicine, account in large part for this calamitous situation. But another major cause for the rapidly increasing health care expenditures is the unforeseen increase in the demand for health care services. This great appetite on the part of the American public is opposed to that of any other country in the world, and it is all fueled by hype from the media leading to very high expectations for satisfaction. And as medical capabilities increase, so will the demand to have access to these capabilities increase.

So, what is to be done? First, what about national health insurance as in England or Canada? I do not believe it will ever work here for many reasons, one being it is far too expensive even in normal times, much less now with a deficit budget crunch. The price tag is $225 billion in new taxes just to start, which is way out of the question. Everyone wants high-quality medicine, the best and newest technology, and free access to unlimited care, but no one wants to pay for it. And no society can afford all that its members are capable of utilizing. When public opinion



A B C D E

Fig 2. Other Founders: (A) Adam Cowley, (B) Ralph Alley, (C) Don Effler, (D) Lyman Brewer, and (E) Don Paulson.

Fig 3. First Officers of The Society: (A) Paul Samson, (B) Tom Burford, (C) Bob Ellison, and (D) Frank Byron.

polls ask "Would you be amenable to be taxed in order to pay for the 37 million uninsured?" the answer is always "yes." But when told it will be at least $200 a year more for everyone and they are already paying more than $2,000 a year per family they say "No." They are willing to pay $50 a year more, but that is not enough. Also, everyone knows that the government cannot do anything cheaper than the private sector. Charlie Mayo in 1938 said "In some other countries, where conditions of living are entirely different from those in the United States, problems of health have been solved by socialization of medicine but to assume that we should imitate those solutions is ridiculous." To have the government be more involved than it already is would, in my opinion, be a colossal catastrophe. And Victor Fuchs, the Stanford health care economist, has pointed out that a general distrust of government by the American people, the heterogeneity of the population, and a less sense of noblesse oblige than in Europe or Canada are all factors that tend to thwart adoption of national health insurance in the United States, at least in the foreseeable future.

By definition a national health service implies planned scarcity of services, or in other words, rationing. Already Canadians are flocking across the border to the United States to obtain services they cannot get at home. And we all know that Americans do not like to stand in line for buses or anything, much less needed medical care.

When one compares the amount of gross national product going for health care in the United States and Canada using the same criteria (apples to apples), there is not a vast difference. And the per capita cost is about the same for both countries.

Public opinion surveys show that many Americans are disenchanted with our health care system primarily because of its cost, and also because of the problems with access and quality in some sectors. Many are advocates of other countries' systems, but few understand the tradeoffs and ramifications inherent if we were to change, and so far the public outcry is not matched by any reasonable solution to fund such a change. On the surface the recent election in Pennsylvania, in which a relative unknown running for the US Senate on a platform of health care for everyone under a national health service plan defeated a well-known politician, was very significant. But when asked "How much will it cost?" the public starts to choke. Those in government who have the audacity (and unfortunately the power) to legislate and regulate the practice of medicine usually do not have the knowledge or expe-

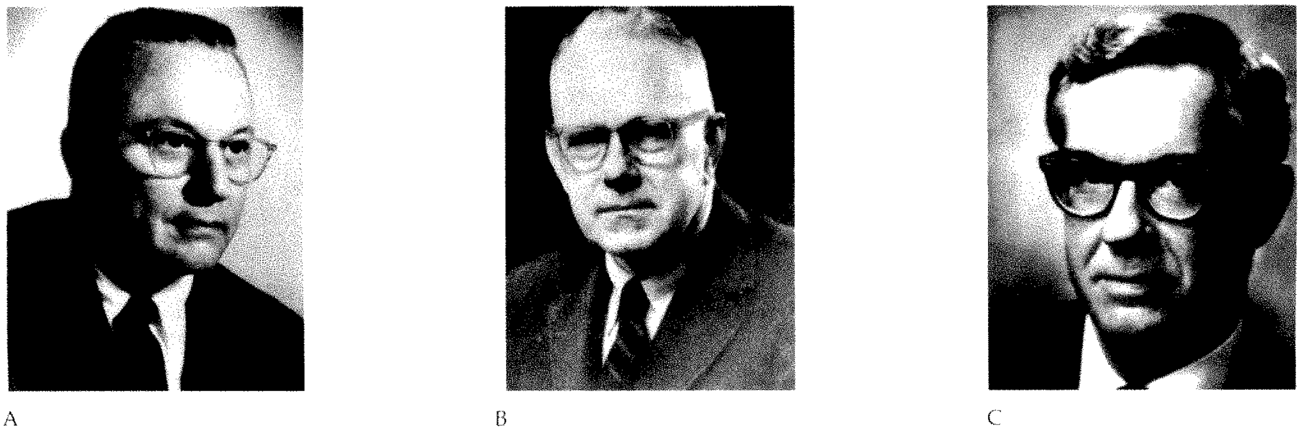


Fig 4. Editors of The Annals of Thoracic Surgery: *(A) John Steele, (B) Herb Sloan, and (C) Tom Ferguson.*

rience upon which to base their case, nor do they accurately predict the public reaction.

Proponents of the single-payor national health insurance plan always point to the relative infant mortality and life expectancy figures to attempt to make their case, as the US looks bad in these categories. However, more important in gauging the quality of health care in a country are lifestyles and environmental factors such as poverty, hard drug use, and teenage pregnancy. When these are studied it becomes obvious that as long as slums, crime, poor housing, and poor education exist so will poor health of poor people. Therefore, it is these societal problems, not medical ones, that are the real culprits, but too often are they laid at our feet.

Germany's system of universal health care coverage works well there because their poverty rate is only 5%, and they are perfectly capable of caring for this small percentage of their population. The same is true of the French. However, 13% of people in the United States live in poverty and another 10% in near poverty, and therein lies the difference.

It is tough enough to be poor, but even worse to be poor once you have been rich, and the great majority of American people (87%) by and large have been rich in the kind of medical treatment they have received. But it is mandatory, with health care costs rising so spectacularly, that the other 13% be covered as well. This may not be as formidable as it appears as two thirds of that 37 million uninsured are in the workplace. Many plans are being espoused both in Washington, DC, and by many states that will achieve universal coverage, not national but universal, and there is a big difference. The great majority keep the system in the private sector with the employers being forced to provide health care benefits to their employees or pay taxes to fund a public plan. And most feel also that the patient must pay something to hold down overutilization, probably by deductibles, copayments, exclusions, and caps. These plans would cost in the realm of $23 billion and are probably doable, in contrast to the $225 billion for a national health service system which, it has been said, would have all the compassion of the IRS, the efficiency of the postal system, and the price tag of the Pentagon.

The rules will probably be made in this decade by the federal government, but it will be the states, each with their own special problems, that will enact the actual legislation focusing on the uninsured and underinsured. It will not come easy, however, as employers hate mandates, doctors and hospitals dislike rules, and the public is against new and more taxation. Furthermore, special interest groups such as the militant affluent elderly (who last year killed a very fair catastrophic insurance bill), organized medicine, labor, and soon even business will all be out with their hatchets blazing. But some compromise is essential unless we are all agreeable to seeing health care eat up 20% of the gross national product in the next few years—which is certainly one short-term solution.

A "managed care" system of health care will evolve simply because the volume of health services is more important than the price paid for them as the usual laws of supply and demand economics seem not to apply to medicine. It should not affect mortality or morbidity but it will be a Chevy, not a Cadillac, and patient satisfaction may drop considerably. The focus, however, is now on the doctors because although our cut of the pie is only 19% of the health care dollar we control 70% of it.

All of this implies a two-tiered system of medicine as there are only three ways to go: (1) to give everything to everybody—there would not be enough resources or money to go around; (2) to give everyone just enough, but not everything, means rationing and implies laws against getting everything—and this simply won't happen; and (3) what must happen is to give everyone a basic package; if they need more, they pay more or the government steps in as I have already mentioned.

The two-tiered system of medicine that will result can be very acceptable, and many of us have lived through it for years. Poor patients who used to be cared for by us for nothing are now done so at tax payor expense to, in my opinion, the detriment of both. Do we surgeons really want the poor uninsured to have universal access to good care? If so, why not give this relatively small group free access to unlimited care free of charge—as we used to do? I think it is time for the medical profession as a whole to do this, and should not the top of that profession—the cardiothoracic surgeon—take the lead? Our specialty, which has recently been looked upon by some, although falsely, as fat cat greedy entrepeneurs, would once again gain favor and respectability in the eyes of the public at large. Granted we are only a small percentage of the whole profession, but just think of the public reaction and the good we would be doing. Even a small dent in the armor of the cost-access-quality dragon might be just the catalyst needed to solve the larger problems and regain the public's respect. We just might end up being heroes after all. It is certainly something we should all be thinking of very seriously.

To paraphrase Winston Churchill and Herman Wouk, the decade of the 1980s in health care could certainly be classified as "The Gathering Storm" and the "Winds of War." Whether the 1990s and beyond will be "War and Remembrance" or "Their Finest Hour" will eventually be up to the medical profession, who will have to see that the best medicine has to offer reaches all of the American people.

With all the constraints placed on the providers, can quality care still be given? I think and hope that it can, as the doctor must always remain the patient's advocate. The quality of care will remain good once patients get to the doctor's office, a hospital bed, an imaging facility, a modern laboratory, or an operating room. What will be rationed is the *access* to that care, and that may not be taken too kindly by the American public. When asked to accept less money for more work (which is inevitable), will doctors deliver quality care or just less care for less money? Again I am confident the answer will be the former. Will patients be educated sufficiently to make intelligent choices in the market place, where they will be for the first time combining affordability, availability, accessibility, and their perception of quality—whatever that may be? This I worry about, as the public can differentiate a mink from a rabbit, a Mercedes from a Volkswagon, but not between doctors except eventually by disease outcomes.

The perception of quality is an elusive thing and often is in the eye of the beholder. Like pornography, as Justice Potter Stewart said, "I can't define it, but I know it when I see it." Doctors know who the good doctors are, but their criteria are very different from those of the public. Leonard Schaeffer, President of Blue Cross of California, gave perhaps the best analogy. When we get on an airplane we assume the pilot went to the Harvard pilot school or we would not get on. What we perceive as quality is "Did they leave on time? Did the stewardess smile? Was the food good? Did they show a movie? Did they lose my luggage?" On the other hand, when patients enter a doctor's office they assume the doctor is the best. What they consider quality is "Did I have to wait too long? Were the receptionist and nurse nice? Did they explain things well? Did they answer my questions? Did the doctor return my phone calls?" And it would behoove us all to keep this in mind. Also, to follow the airplane analogy somewhat further, we are all going to get there, but some will be riding first class and others will be in the back of the plane.

Now to gaze into my crystal ball. I feel like my favorite philosopher, Yogi Berra, who said, "it's hard to predict anything, especially the future." Nevertheless, here goes.

1. Health care spending will continue to increase, but at a slower rate.
2. The two main players who will eventually decide health care policy and demand major legislation are the business community and middle-class America. When medical costs rise to the extent that profits are jeopardized, and when an average family is spending a quarter to a third of its income on health insurance, something will happen. That is *if* they can decide *what* they want, which will not be easy. There probably will be no major changes and no universal health care coverage until later in the decade in spite of the Pepper Commission findings and in spite of the many health care bills being introduced by the Democrats. The reasons behind my reasoning are (a) the many special interest groups, (b) anything done will cost somebody a lot of money, and (c) because everyone's second choice is the status quo. Some things will be accomplished in increments such as malpractice insurance reforms, increased Medicaid benefits, and physician payment reform, which is already underway.
3. The key conflicts of the future will be (a) public versus the private sector, (b) federal government versus state governments, (c) competition versus regulation, and (d) the poor versus the non-poor.
4. Alliances between doctors and hospitals will increase, while more and more hospitals close and the smart ones will merge and specialize and stress outpatient services.
5. Payors, be they government or private, will continue to put restraints on doctors and hospitals to hold down rate increases.
6. Quality of care will be monitored by disease outcomes, and practice guidelines will become more and more important as payors will use outcomes and practice parameters to decide if certain procedures warrent coverage.
7. Large multispeciality group practices will become the wave of the future as the best vehicle to deliver cost-effective medicine and the best way to increase market share.
8. "Managed Care" will become the watchword in the marketplace, and our patients will not like it.
9. And if nothing else is done, it is mandatory that we encourage the individual to be responsible for his or her health as well as his or her health care costs if we are to see some light at all at the end of the tunnel. So much for predictions.

I trust that you are all aware that Aesculapius, the God of Medicine, was the son of Apollo, and Apollo was the son of Zeus. And, therefore, doctors are the direct descendants of God. People used to believe that, as physicians always ranked at the top of the polls of "the most admired" with a 95% rating. We are still near the top but only at about 70%, which I presume means that 30% of the people do not like anybody.

It is tragic, however, that as medical science has advanced beyond our wildest dreams, an adversarial relationship has developed between doctor and patient. Why? Outrageously high fees charged by a few selfish physicians are certainly one factor. But it is interesting to note that whereas success among peers in business is gauged by the acquisition of wealth gained ethically and legally, this is not so with doctors, and is often the reverse. Another reason for the loss of confidence by the public is that we have allowed expensive machines and equipment to separate us from our patients. But I believe the most important factor is that we have lost the art of communication, which is the essence of the art of medicine, and if not the art, why the science? The art is a precious commodity that can be translated to mean the confidence and trust of the individual patient or the public at large. We must learn to emulate the old horse and buggy doctor (Fig 5) who sat up all night just watching grandma die—and the family revered him. Now we save grandma's life, but the love and respect we once enjoyed as a profession is gone. But although the public does not like doctors as a group, most still love their own doctor—and this is something to build upon.

Hippocrates held that the knowledge of the body depends upon the knowledge of the whole man. Back in 1938 Will Mayo deplored the fact that ". . . .The highly scientific development of this mechanistic age. . . .[has] tended to make the patient not the hub of the wheel, but a spoke." Medicine has never veered from its primary tenets of *Primum Non Nocere*, its respect for life, and for the quality of life. But we may have strayed from our previous empathetic nature, and at worse without an empathetic stance, care of the patient may even be driven

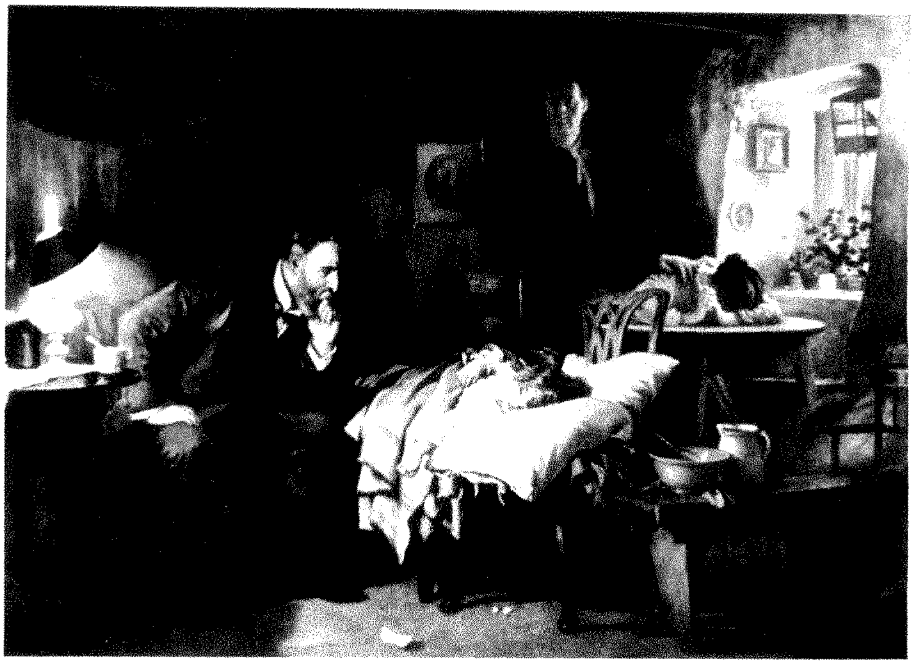


Fig 5. "The Doctor" by Sir Samuel Luke Fildes, 1891 (The Tate Gallery, London).

by financial factors rather than by the clinical needs of the patient.

Empathy embodies good hearing as well as good listening, a positive nonjudgmental attitude, and not being afraid to open ourselves to our own emotions. It is being compassionate and communicative while not showing pity and is filled with warmth, helpfulness, and caring. And it is learning our patient's needs and wants, and to comfort with kindness (Fig 6).

We must teach our students that the patient is a subject not an object; that high touch is as important as high tech; that curing and healing are not the same; and that they must be doctors, not just surgeons. Unfortunately this art of communication cannot always be imparted, and again Will Mayo in 1931 said "One meets with many men who have been fine students, and have stood high in their classes, who have great knowledge of medicine but very little wisdom in application. They have mastered the science, and have failed in the understanding of the human being." These prophetic words were uttered 60 years ago and apply even more today. Although much of the art of medicine is taught now, as in the past, by mentoring and role modeling, it is difficult and just possibly is unteachable. That is why I have been telling admission committees to medical schools that they need to take more "B+" students who were born to be empathetic people, not merely straight "A" ones who cannot communicate. And, of course, we would all like to be like Marcus Welby who, as Dr William Kissick has pointed out (1) always made the correct diagnosis, (2) always was nice to patients and colleagues, (3) never lost a patient, (4) never was sued for malpractice, and (5) did well financially on one patient a week.

We must realize, too, that patients have become more knowledgable and sophisticated and no longer take everything we say as gospel. They have learned to question and to expect answers, to ask others for advice, and to take an active part in their diagnosis and treatment. They expect explanations in lay language of not merely what and where, but how and why. And it is our duty to fulfill

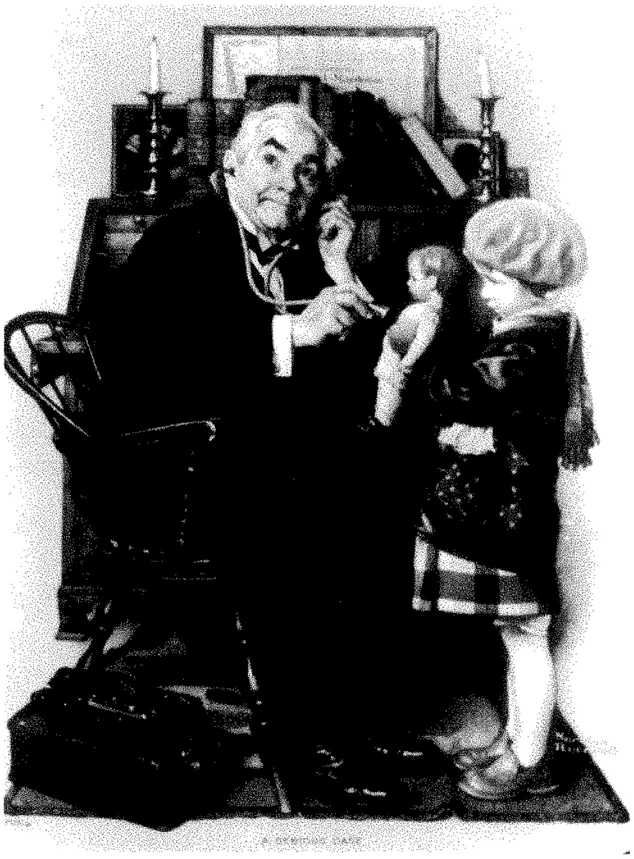


Fig 6. The art of medicine. (© Curtis Publishing Company.)

those expectations. If we are not born with these interpersonal and communicative skills, we had better learn them, if possible, if we are to effectively practice the art that is so precious to the patient. The goal may be our patients' satisfaction with the realization of their own expectations, and this depends on the outcome of the solution to their problems—real or imagined. With the proper communication and concern the patients will become our advocates, and we need them now more than ever. I might also add that if we are successful in this the number of malpractice suits will drop dramatically even in the presence of poor, but unavoidable, results.

Because of the incredible technology now at our fingertips, philosophical questions arise whether to allow what used to be called "God's Will," or pneumonia ("the old man's friend") to prevail or not. Undoubtedly ethical questions like this will demand more focus in the years to come, and we must approach them with an open mind, and one in which the doctor and the patient and the family enter into a very personal relationship. Even though it is sometimes hard for surgeons to do nothing, it may often be the right thing to do. The dilemma is often should we put the patient through the pain of and the recovery from operation to live a short time when the costs may prevent an offspring getting a college education. And it is in the setting of the intensive care unit where probably the need for protecting and enhancing human dignity becomes the greatest. It is as important for the family as for the patient to learn to deal with the crisis, and it is where the surgeon can shine by incorporating caring behavior with scientific skill.

We are in a service-oriented profession, but one that is very unique in its intimacy. For years we built on and were respected for this very intimacy, which for various reasons has now been eroded. The environment in which we work, the hospital and the office, does not foster this intimacy. It is often impersonal and cold, with paper gowns open at the back, claustrophobic MRIs, and bodies marked with purple ink, and where unfamiliar and undecipherable medical language is spoken. Also, to share a room with a stranger, or several strangers, in a hotel or motel when we are well would not be tolerated, so why should it be condoned in a hospital when we are sick? If we are to have concern for the dignity of the individual patient we must strive to make his environment more humane and have increased awareness of his concerns and feelings.

We must realize the patient is frightened and vulnerable; we must involve him more in the facts concerning his illness, seek his opinions, discuss alternatives, and make common decisions. We should never lie, but neither should we let him give up hope, for miracles do happen. And at all times we must show patience and respect. All of this combines to be the essence of the art of medicine, and without it the science pales. With it is embodied the noblest profession of them all.

In the 21st century I believe it will be the surgeon-scientists who will command the respect, envy, and esteem that should rightfully be theirs, but only if they show at the same time the empathy, warmth, and concern for the patient that is our legacy. This should be the goal toward which every young cardiothoracic surgeon in this audience and elsewhere should aspire, and I am confident that you will. Hippocrates ends his oath with "While I continue to keep this oath unviolated, may it be granted to me to enjoy life and the practice of the art, respected by all men, in all times!" It is even more timely now than it was then.

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Skeletal Muscle Ventricles in the Pulmonary Circulation: Up to 16 Weeks' Experience

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Skeletal muscle ventricles (SMVs) were constructed from the right latissimus dorsi muscle of 8 mongrel dogs. After a 3-week vascular delay period, each SMV was electrically preconditioned with 2-Hz continuous stimulation of the thoracodorsal nerve for 6 weeks. A porcine-valved conduit was then anastomosed between the right ventricle and the SMV, with a second valved conduit connecting the SMV to the main pulmonary artery. The pulmonary artery was then ligated proximal to the conduit. The SMVs were stimulated to contract in 1:2 diastolic mode with a 33-Hz burst frequency. Effective right ventricular assist was achieved in all dogs. Cardiac output increased by 22.6% (1,799 ± 97 versus 1,467 ± 84 mL/min; $p < 0.001$), systemic systolic arterial pressure by 9.3% (90.1 ± 3.5 versus 82.4 ± 3.9 mm Hg; $p < 0.005$), and peak pulmonary artery pressure by 31.8% (27.8 ± 2.0 versus 21.1 ± 1.7 mm Hg; $p < 0.001$) at the initiation of this study. In 6 dogs, effective right heart assist was sustained for periods of between 1 week and 12 weeks. Two dogs survived for longer than 3 months, though with evidence of deteriorating SMV function. These results demonstrate the feasibility of providing sustained right ventricular assist using this modified "Rastelli-SMV" configuration, which obviates the limitations imposed by low right atrial preload.

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One of the main disadvantages of skeletal muscle that frustrated early attempts to provide cardiac assistance was muscle fatigue. The demonstration that muscle can, with appropriate electrical conditioning, be converted to a fatigue-resistant form has largely overcome this problem [1]. We have subsequently shown that skeletal muscle ventricles (SMVs) constructed from canine latissimus dorsi muscle are capable of a level of continuous cardiac-type work that, under appropriate loading conditions, exceeds that of the right ventricle. We [2] have also demonstrated that SMVs can continue to function effectively in the circulation for periods of up to 18 months without detriment.

Attempts to provide right heart assist have previously been frustrated by low right atrial pressures, which supply an inadequate preload to allow optimal SMV function. We [3] have recently shown in acute studies that a modified "Rastelli-SMV" configuration is able to exploit right ventricular pressure to satisfy SMV preload requirements, thus permitting effective right heart support to be generated. The purpose of the present study was to determine whether this new right heart configuration could remain effective over the long term.

Material and Methods

Skeletal muscle ventricles were constructed from the right latissimus dorsi muscle of 8 mongrel dogs weighing between 18 and 23 kg. Animals received humane care in accordance with the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Anesthesia was induced by intravenous administration of thiamylal sodium (12 to 18 mg/kg) and maintained by inhalation of isoflurane (1% to 2%). Preoperative and postoperative antibiotic prophylaxis (cefazolin sodium, 1 g intravenously at operation followed by 750 mg orally twice daily for 1 week) was administered. In the early postoperative period, pain was controlled with intravenous buprenorphine hydrochloride (0.02 to 0.04 mg/kg). After the connection to the circulation was done, the animals were given heparin sodium (2,000 units subcutaneously) twice daily for the first 3 days and then warfarin sodium (4 mg) daily for anticoagulation.

Skeletal Muscle Ventricle Construction

The right latissimus dorsi muscle was dissected from surrounding tissues with the neurovascular pedicle left intact. This was achieved by dissecting the muscle from the spine, chest wall, platysma, teres major, and triceps. The humeral insertion was left intact to protect the neurovascular pedicle. All collateral blood vessels arising from the skin, chest wall, and adjacent muscles were ligated and divided. A modified unipolar cuff nerve electrode (model 6901; Medtronic, Inc, Minneapolis, MN)

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was placed around the right thoracodorsal nerve. The muscle was then wrapped in a spiral fashion around a cone-shaped Teflon mandrel (length, 9 to 10 cm; volume, 55 to 60 mL). A Teflon felt sewing ring (USCI, Billerica, MA) was connected to the ventral end of the mandrel, and each layer of the ventricle was sutured to the sewing ring, securing the mandrel in place.

The nerve electrode was connected to a unipolar neurostimulator (Itrel model 7421; Medtronic, Inc) placed under the right rectus abdominis muscle. The subcutaneous tissue and skin were closed over the SMV, which had been placed on the outside of the chest wall. The SMV was left undisturbed for 3 weeks to allow its collateral blood supply to recover [4].

After the 3-week vascular delay period, the stimulator was activated with a transcutaneous programmer (model 7431; Medtronic, Inc). All SMVs were preconditioned with 2-Hz continuous frequency, resulting in 120 twitches per minute. The individual electrical pulses were of 210-μs duration and had an amplitude of two to three times threshold, ranging from 1.0 to 2.0 V. Electrical stimulation was continued for 6 weeks to provide muscle transformation to a more fatigue-resistant state.

Connection to the Circulation

After the electrical preconditioning period, a second-stage procedure was performed. The animals were anesthetized again as already described. A second incision was made over the most ventral aspect of the SMV, and the Teflon mandrel was removed.

The heart was exposed through a median sternotomy. Two screw-in epicardial electrodes (SP 5548; Medtronic, Inc) were placed on the left ventricle to allow synchronization of SMV contraction to the R wave of the electrocardiogram. A 16-mm porcine-valved composite Dacron graft (Hancock, Medtronic, Inc) was connected between the right ventricular outflow tract and the SMV (afferent limb), and a similar conduit was used to connect the SMV to the main pulmonary artery (efferent limb) (Fig 1). This was achieved with side-biting vascular clamps and without cardiopulmonary bypass. No artificial lining was used within the SMV cavity itself, apart from the smooth fibrous inner reaction layer induced by the Teflon surface of the mandrel over several weeks. The animals were systemically heparinized (100 U/kg intravenously) before release of the clamps. Ligation of the proximal main pulmonary artery with umbilical tape ensured obligatory flow through the SMV. Totally implantable 16-mm ultrasonic flow probes (Transonic Systems, Inc, Ithaca, NY) were placed around the outflow conduit and ascending aorta in all dogs. Connector portions of the flow probes were placed subcutaneously in the neck for later access. All dogs received autologous blood transfusions during the course of the operation.

Skeletal Muscle Ventricle Stimulation Protocol

After the SMV was connected to the circulation, the Medtronic Itrel pacemaker was replaced with an implantable rate-responsive, synchronized pulse train stimulator (Prometheus; Medtronic, Inc) [5]. The pacemaker was programmed to deliver a 33-Hz burst frequency, 25% to 30% of R-R interval burst duration, 3-V amplitude, and 50% to 60% of R-R interval delay. The pacemaker was programmed to stimulate the SMV at 1:2 when the heart rate was less than 160 beats per minute and 1:3 when it was greater than 160 beats per minute.

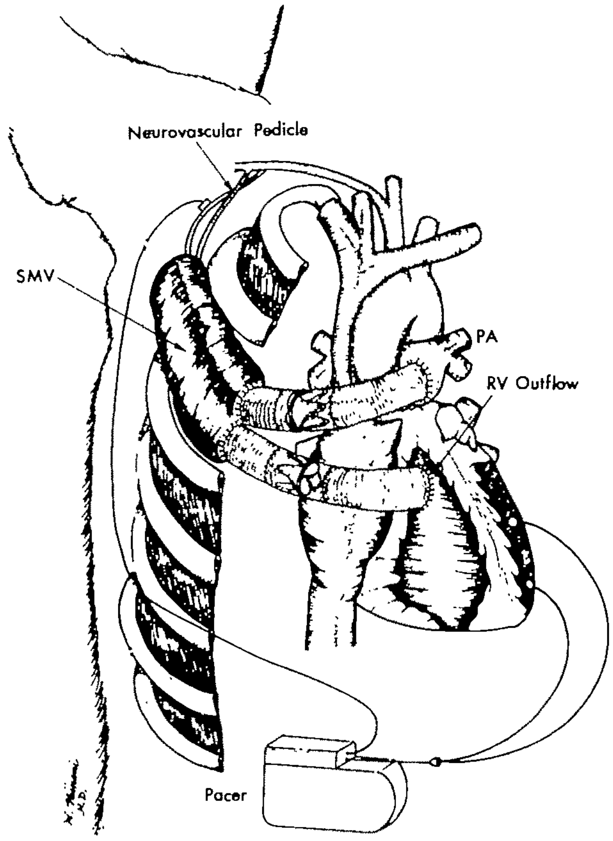

Fig 1. The surgical configuration. The skeletal muscle ventricle (SMV) is on the outside of the chest wall. The main pulmonary artery (PA) has been ligated proximal to the anastomosis. (RV = *right ventricular.)*

Measurements

Femoral artery pressure, ascending aortic flow, pulmonary artery pressure, SMV pressure, and central venous pressure were measured. Five-French microtransducer-tipped catheters (Millar Instruments, Inc, Houston, TX) were placed in the SMV and in the main pulmonary artery. Ultrasonic flow probes were connected to a two-channel flowmeter (T-201; Transonic Systems, Inc) for the measurement of pulsatile and average flow. After the initial measurements, all catheters were removed, a 28F chest tube was placed in the pleural space in all animals, and the chest was closed in layers. The dogs recovered from anesthesia without difficulty. Drains were removed by the third postoperative day.

Subsequent hemodynamic measurements, including femoral artery pressure, SMV pressure, pulmonary artery flow, and ascending aortic flow, were repeated under general anesthesia at 1 week, 2 weeks, 3 weeks, 4 weeks, and monthly intervals thereafter.

Table 1. Surgical Outcome

Dog No.	Length of Survival	Cause of Death
1	24 h	Blood loss
2	24 h	Blood loss
3	18 d	Pleural effusion
4	13 d	Pleural effusion
5	17 wk	Euthanized
6	13 wk	Euthanized
7	4 d	Pleural effusion
8	5 wk	Euthanized

Calculations

Stroke work of the SMV was calculated as the product of stroke volume and mean SMV developed pressure during SMV contractions. Power output of the SMV was calculated as the product of SMV stroke work and SMV contraction rate. Stroke volume of the SMV was calculated from the integrated pulmonary artery flow curve. Mean SMV developed pressure was calculated from the integrated SMV pressure curve. Integration of the flow and pressure curves was performed with a digitizing pad (GAP1; GTCO Corp, Rockville, MD) and a portable computer (T3200SX; Toshiba, Irvine, CA).

All data given represent the mean ± the standard error of the mean. Statistical analysis was carried out with the Wilk-Shapiro test for normality. Student's t test was performed on paired data with RS/1 software (copyright 1986, Bolt Beranek and Newman Inc, Cambridge, MA) on a portable computer (T3200SX).

Results

The 8 dogs were operated on consecutively and are numbered in that sequence. Individual survival and associated complications are listed in Table 1. The first 2 dogs died of blood loss within 24 hours after operation. The remaining 6 dogs recovered well, regaining their preoperative level of activity by the third postoperative day. They were tether free in that no tubes or wires crossed the skin barrier.

At the time of the initial measurement, pulmonary artery pressure was increased by 31.8% with the stimulator on compared with the stimulator off (27.8 ± 2.0 versus 21.1 ± 1.7 mm Hg, n = 8; $p < 0.001$). The central venous pressure was slightly decreased during pacer on compared with off, but this failed to achieve significance (6.7 ± 0.7 versus 6.9 ± 0.8 mm Hg).

Cardiac output observed during SMV stimulation is shown in Figure 2. At the initial measurement, the degree of augmentation with the stimulator on was 22.6% (1,799 ± 97 versus 1,467 ± 84 mL/min, n = 8; $p < 0.001$); at 1 week, it was 16.3% (1,678 ± 68 versus 1,443 ± 71 mL/min, n = 6; $p < 0.005$); and at 3 weeks, it was 11.6% (1,972 ± 155 versus 1,767 ± 138 mL/min, n = 4; $p < 0.005$). Figure 3 illustrates these changes.

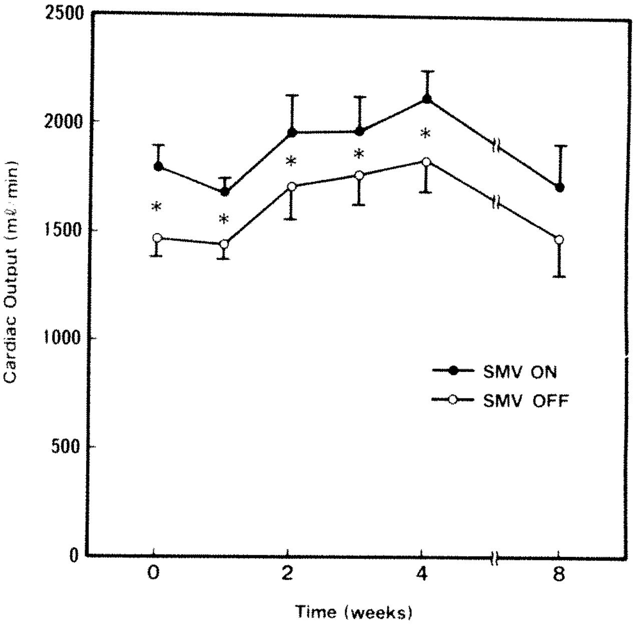

Fig 2. Cardiac output for the group over time. SMV ON *indicates stimulation of the* skeletal muscle ventricle *(SMV) with 33-Hz burst stimulation.* SMV OFF *indicates no stimulation of the SMV. (*p < 0.05).*

Systolic arterial pressure initially increased by 9.3% (90.1 ± 3.5 versus 82.4 ± 3.9 mm Hg, n = 8; $p < 0.005$), by 7.0% (114.9 ± 8.8 versus 107.4 ± 6.3 mm Hg, n = 6; $p < 0.005$) at 1 week, and by 5.2% (110.4 ± 7.5 versus 104.9 ± 8.6 mm Hg, n = 4; $p < 0.05$) at 3 weeks (Fig 4).

Functional variables for the SMV are shown in Figures 5 through 8. For technical reasons related to the composition of the Dacron conduit, the ultrasonic flow probe failed to record pulmonary artery flow at the time of the

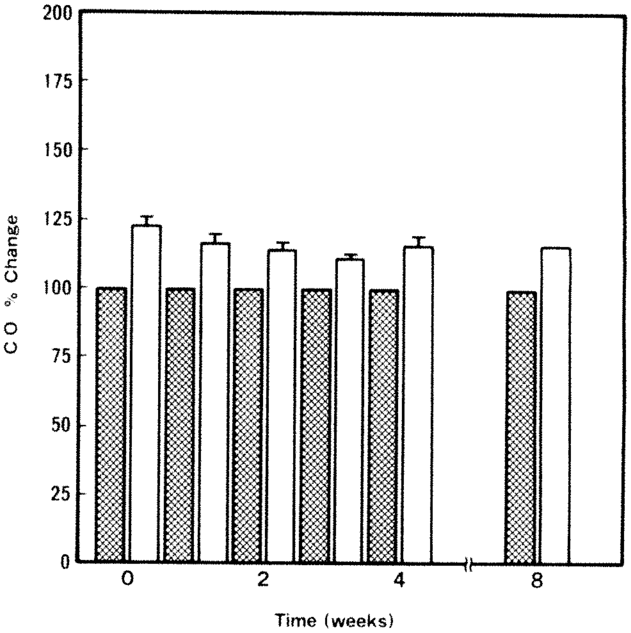

Fig 3. Augmentation of cardiac output (CO) with stimulator ON (open bars) *expressed as a percentage of measurements with stimulator OFF* (hatched bars) *over time.*

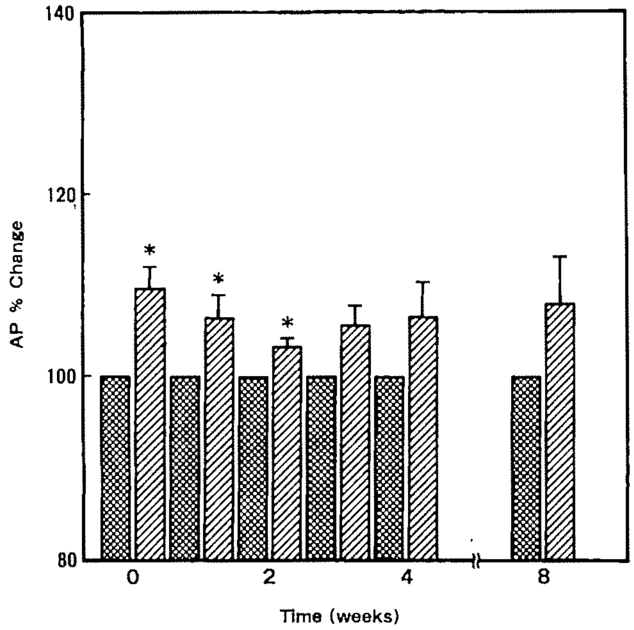

Fig 4. Augmentation of systolic arterial pressure (AP) with stimulator on (diagonally striped bars) *expressed as a percentage of measurements with stimulator off* (hatched bars) *over time.* (**p* < 0.05).

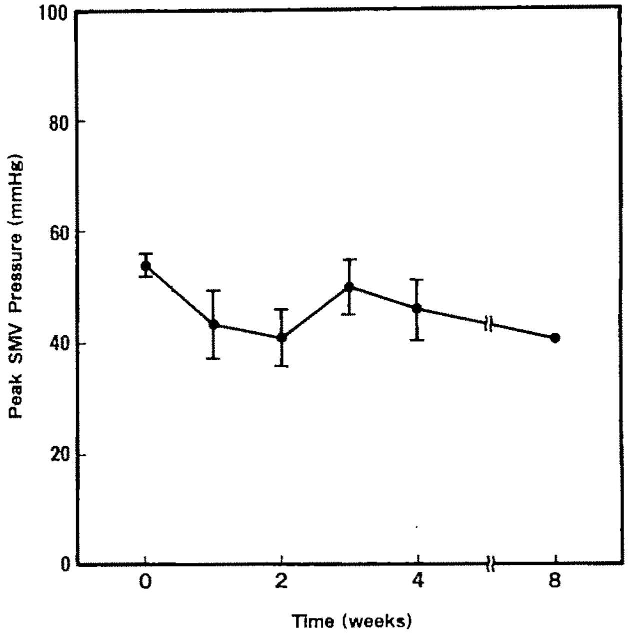

Fig 6. Peak skeletal muscle ventricle (SMV) pressure recorded during SMV stimulation.

initial operation. Thereafter, SMV flow was successfully recorded, and results are shown in Figure 5. At 1 week, SMV output was 807.9 ± 71.7 mL/min (n = 6), and at 3 weeks it was 1,028.9 ± 165.8 mL/min (n = 4). Peak developed SMV pressure was initially 54.0 ± 2.1 mm Hg (n = 8), and this was sustained at 3 weeks (50.0 ± 5.02 mm Hg, n = 4) (Fig 6).

Skeletal muscle ventricle stroke work after 1 week of continuous pumping was 0.31 ± 0.01 × 10^6 ergs (n = 6), and at 3 weeks it was 0.35 ± 0.07 × 10^6 ergs (n = 4) (Fig 7A). Normal canine right ventricular stroke work for this size of dog is 0.22 ± 0.11 × 10^6 ergs [4]. Figure 7B shows individual stroke work values for the 3 dogs whose SMVs functioned well over the first month. Therefore, these SMVs generated stroke work that was equal to or greater than the stroke work of the canine right ventricle. Because the SMVs mostly contracted at a rate of 1:2 with the heart, their overall power output was less than the power output of the canine right ventricle, which is 0.064 ± 0.032 W [4]. The SMV power output was 0.033 ± 0.002 W at 1 week (n = 6) and 0.046 ± 0.008 W at 3 weeks (n = 4) (Fig 8).

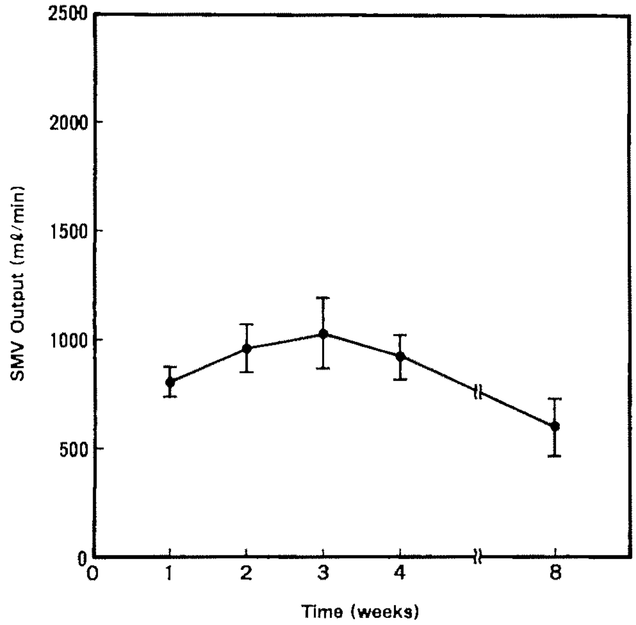

Fig 5. Skeletal muscle ventricle (SMV)-generated output over time.

Figure 9A shows initial recordings from 1 dog at the commencement of right heart assist with an SMV and Figure 9B, similar data from the same animal after 1 month of continuous pumping.

Three dogs survived for more than 1 month (dogs 5, 6, and 8), and 2 of them (dogs 5 and 6) survived for more than 3 months. These 2 dogs did not show any apparent disability. Their SMVs functioned well for up to 3 months. However, after 3 months, the degree of augmentation started to deteriorate. These dogs were euthanized at 1 month (dog 8), 3 months (dog 6), and 4 months (dog 5) postoperatively. Postmortem examinations were performed on dogs 3 through 8. Extensive collateralization was noted between the SMV and the adjacent subcutaneous tissue and chest wall. The SMVs appeared to have retained their initial size except in the 2 dogs surviving longest (dogs 5 and 6). The muscle in both the inner and outer layers appeared healthy. Four animals had no evidence of thrombus formation within the SMVs or conduits. In 2 dogs (dogs 3 and 4), through thrombus was found within the apex of the SMV, it was firmly adherent to the wall. In no animals were thrombi found within the pulmonary vessels, and none of the dogs showed histological evidence of pulmonary infarction. In the 2 dogs surviving longest, however, there was a discouraging finding. In both, the SMVs were shrunken, with a greatly reduced cavity size. Histologically, there was evidence of some degenerative changes in the muscle, which were mainly confined to the innermost layer. The histological study was otherwise unremarkable.

Comment

Skeletal muscle has an ability to adapt to altered demands by transforming its biochemical and structural characteristics. A clearer appreciation of this property has recently stimulated interest in its use for cardiac assistance.

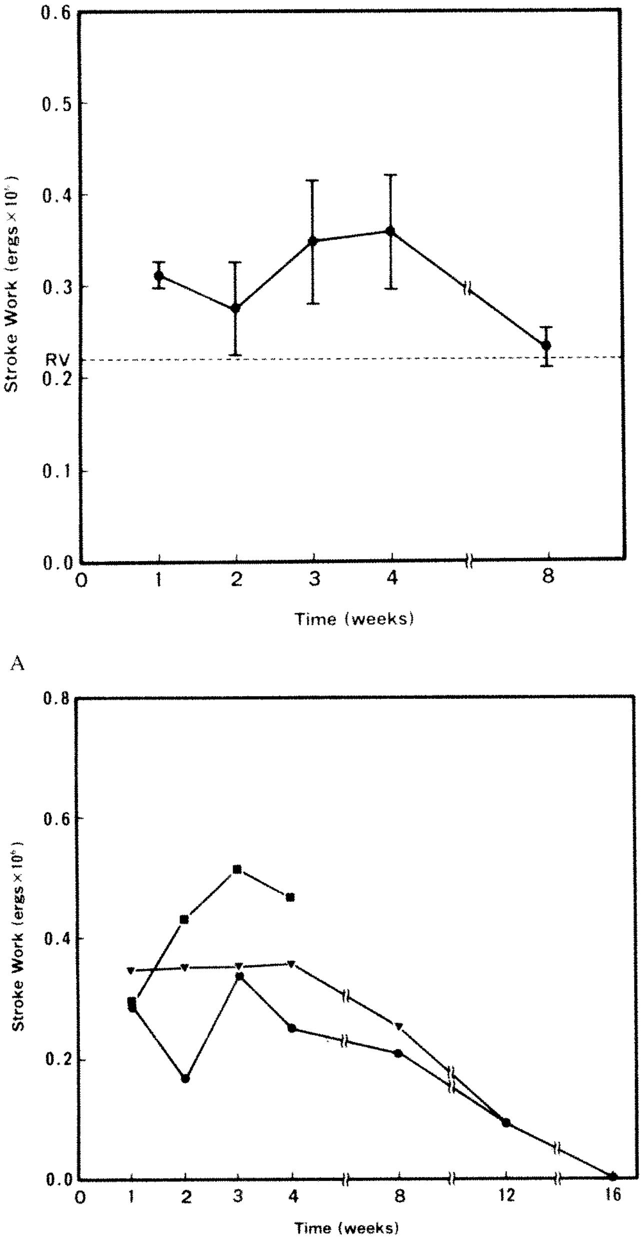

Fig 7. Skeletal muscle ventricle stroke work as a function of time. RV indicates the value for normal canine right ventricular stroke work. (A) The stroke work for all animals is shown. (B) The stroke work for 3 dogs that survived more than 1 month is shown.

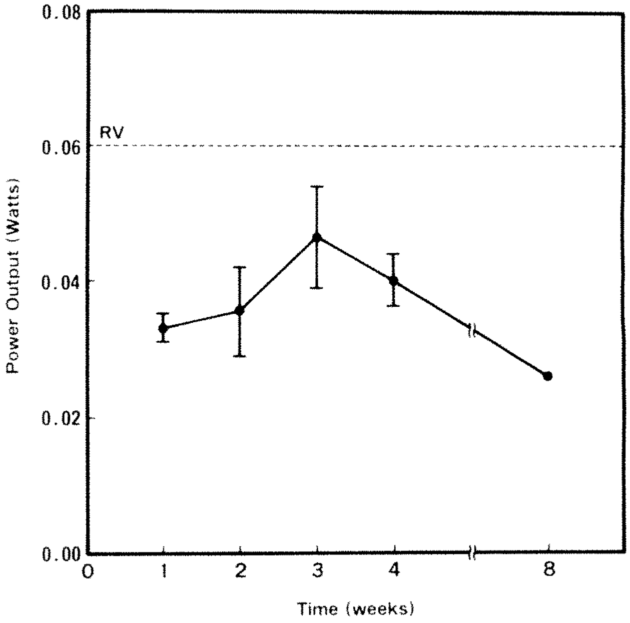

Fig 8. Skeletal muscle ventricle power output as a function of time. RV indicates normal canine right ventricular power output.

Studies [6, 7] using a mock circulation device have demonstrated the capability of SMVs to generate a level of power equal to or exceeding that of the canine right ventricle. Other studies have reproduced this success in the circulation, even to the point of totally replacing right heart function with SMVs in short-term experiments [8–10]. This was achieved by an arrangement that bypassed the right ventricle, and because the experiments relied on right atrial pressure for SMV preload, this had to be appreciably elevated for satisfactory SMV function. For this reason, animal survival beyond a few hours has not been reported in this setting. In contrast, survival beyond 18 months has been achieved with an SMV in the systemic circulation, where it functioned as an arterial diastolic counterpulsator and was therefore able to take advantage of a higher preload [2].

We have recently addressed the problem of the relatively high preload requirements of SMVs by evaluating a new right heart assist configuration that exploits right ventricular rather than right atrial pressure. The configuration used in this study is based on the concept of a right ventricle to pulmonary artery valved conduit proposed originally by Rastelli [11]. Preliminary acute studies [6] have been reported previously, and effective right heart assist at normal filling pressures has been documented. The present study has demonstrated that the "Rastelli-SMV" configuration can pump blood continuously and effectively in the pulmonary circulation for up to 3 months. Moreover, the SMVs were capable of generating stroke work exceeding that of the right ventricle throughout this period. Thromboembolic complications were not a major problem in this study.

The findings of the present study suggest a potential

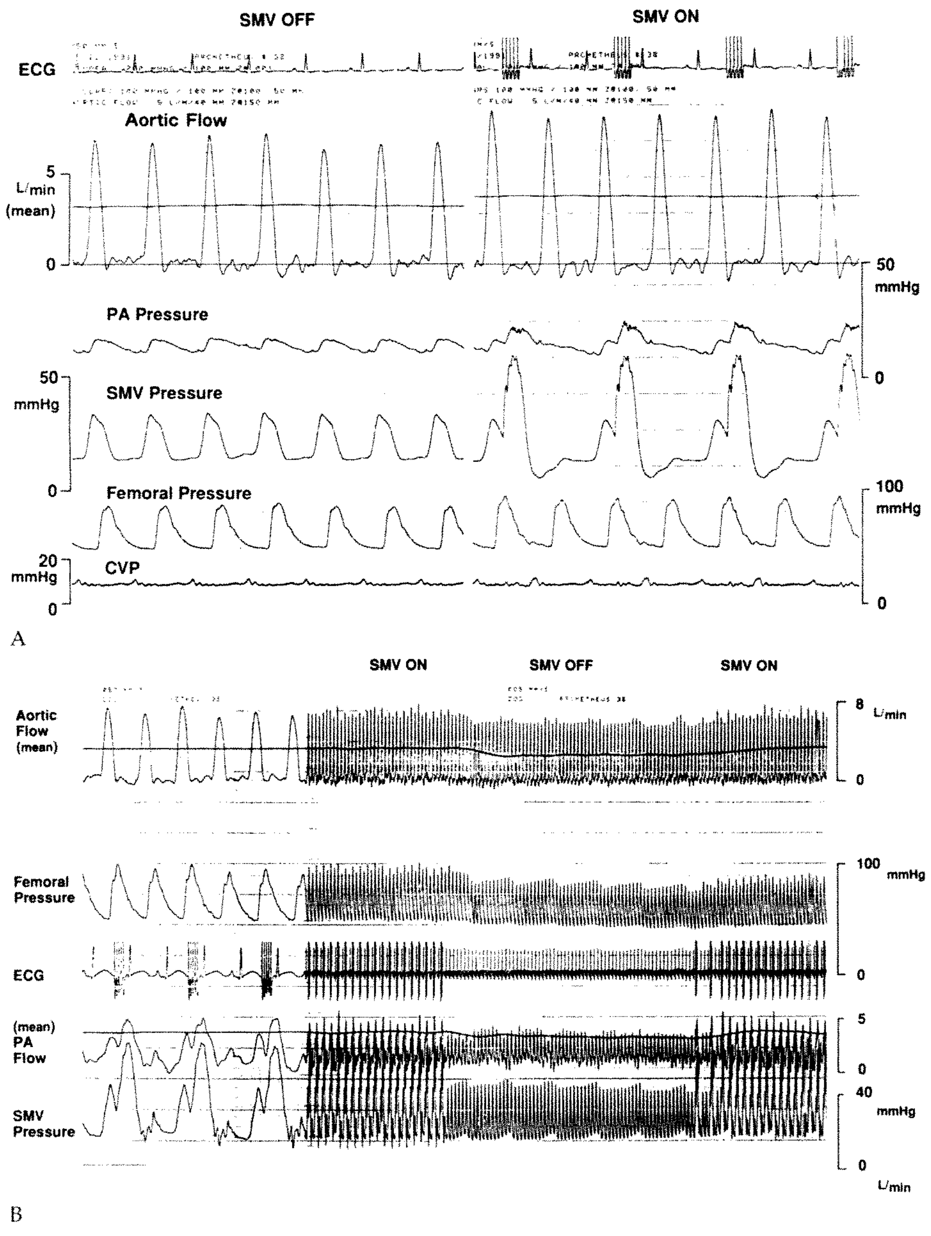

Fig 9. (Dog 5.) Representative hemodynamic tracings recorded during stimulator on (SMV ON) *and off* (SMV OFF)*: recorded at (A) the time of operation and (B) 1 month after operation.* (CVP = *central venous pressure;* ECG = *electrocardiogram;* PA = *pulmonary artery;* SMV = *skeletal muscle ventricle.)*

application for the SMV in the face of right-sided cardiac impairment. Although not investigated in the present study, the configuration we used may have particular application in conjunction with an elevated pulmonary vascular resistance. An experimental model of pulmonary hypertension with cardiomyoplasty has been previously described [12] and would be an interesting avenue for future studies. Most experimental and clinical studies of right heart assistance, such as intrapulmonary arterial balloon pumping or artificial ventricular assist devices, are mainly aimed at the treatment of acute right ventricular failure [13–17]. One of the major limitations for long-term use of such devices is their requirement for a bulky external power source. Because skeletal muscle has its own built-in power source, it potentially offers a more appropriate means for achieving permanent right heart support.

Starr and associates [18] originally proposed that the right ventricle was dispensable and simply served as a passive conduit for blood flow from the systemic venous system to the pulmonary circulation. This belief was derived from experiments in dogs in which complete destruction of the right ventricular free wall resulted in no detectable impairment of right ventricular pressure development or overall cardiac performance. This concept was the underlying basis for the development of the Fontan procedure [19].

During the last decade there has been some refinement of this concept, and the functional importance of the right ventricle has now become apparent, particularly in situations where pulmonary vascular resistance is elevated [20]. Under such circumstances, volume loading the circulation may not provide sufficient preload for satisfactory left heart function. In addition, some patients are not candidates for the Fontan procedure because of an elevated pulmonary artery pressure. Mayer and associates [21] reported a 100% mortality for this procedure in the presence of a mean pulmonary artery pressure higher than 15 mm Hg and a pulmonary vascular resistance greater than 2 U/m^2.

In the present study, SMVs were capable of generating stroke work greater than that of the right ventricle for 2 months (see Fig 7A). As shown in Figures 9 and 10, the SMV's preload was between 5 and 10 mm Hg, which is within the normal range of the central venous pressure. However, we did encounter a potentially serious problem. Two of the dogs surviving longest, both alive more than 3 months after operation, exhibited a progressive reduction in SMV size that was apparent on external examination and accompanied by deteriorating SMV function. A greatly reduced SMV cavity size, which was not the result of mural thrombus formation, was found at postmortem examination. This problem has not been observed in SMVs connected to the systemic circulation, even after 18 months of continuous pumping, which suggests that it may be a pressure-related phenomenon. It is possible that because SMVs lack a skeleton, the relatively low pressures of the pulmonary circulation are inadequate to maintain optimal resting muscle fiber length, resulting in compensatory shortening of the muscle, which in this case would reduce overall chamber size. Such muscle shortening is a familiar problem in orthopedic practice. In theory, this may not occur in situations where pulmonary vascular resistance is elevated, as higher intracavitary pressure may more effectively splint the SMV, as it appears to do in the systemic circulation.

In conclusion, this study has demonstrated that SMVs are capable of substantial and continuous stroke work while pumping blood in the pulmonary circulation over several weeks. Although there are still problems to be overcome, this configuration might have a potential clinical application for any condition of the myocardium or pulmonary circulation that affects right ventricular contractile function. For example, certain congenital heart defects or right ventricular failure secondary to pulmonary hypertension may prove suitable for such a form of circulatory assistance.

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DISCUSSION

DR RICHARD D. WEISEL (Toronto, Ont, Canada): Thank you for a very innovative report from a group who has contributed to this important area for many years. I would like to request questions from the floor. Perhaps while you are preparing your questions, I will ask for a clarification. I gather from your presentation that you found no evidence of pulmonary infarction. Is that correct?

DR NIINAMI: Correct.

DR WEISEL: In previous studies on left ventricular assist device your group has suggested that the aorta must be ligated to permit total circulatory flow to pass through the pump to avoid thrombi. Did you also find the same problem in the pulmonary circulation? Must you ligate the pulmonary artery to avoid pulmonary emboli in your model?

DR NIINAMI: With earlier experiments, we did not ligate the pulmonary artery and not as much blood flowed to the SMV. Therefore, we subsequently ligated the pulmonary artery to get improved blood flow to the SMV.

DR CARLOS G. DURAN (Riyadh, Saudi Arabia): This is a very elegant experiment. There is one thing I do not quite understand. Your right ventricle is normal, right?

DR NIINAMI: Yes.

DR DURAN: And you are having a systolic filling of your SMV?

DR NIINAMI: Yes.

DR DURAN: Now, how is it going to help in a clinical setting, because you need the right ventricle to pump into the SMV and then the SMV to pump in diastole, right?

DR NIINAMI: Yes.

DR DURAN: So if you have a severe failure of the right ventricle, how are you going to get a good filling of your SMV?

DR NIINAMI: Actually, from our mock circulation study, the SMV can function with lower filling pressure, so we believe with a low filling pressure, the SMV should also function well. However, in profound right heart failure the filling pressures for the SMV would be high and that should present no problem to the SMV. If the right heart failed completely, it is likely the left ventricle would also fail completely, because they share a common septum, and that would be a major problem for both the SMV and the patient!

DR DURAN: Don't you think it should have been connected to the right atrium?

DR NIINAMI: This has been tried in other experiments.

DR DURAN: What happened then?

DR NIINAMI: When the SMV is outside of the chest the compliance is a little bit lower than in the chest SMV. This has been proven using a mock circulation study. We therefore put the SMV inside the chest and improved the diastolic function. After it was put inside of the chest, the SMV functioned well even under a very low preload setting. So this is the kind of step needed to go from the right atrium to the pulmonary artery. We believe that even under a low preload setting, an SMV inside the chest can generate a good flow and pressure.

DR WEISEL: The other question I have for your group regards the pulmonary vascular resistance. Your experiments were performed on animals with normal right ventricles with a low pulmonary vascular resistance. What would happen if the pulmonary vascular resistance were high? Have you tried to increase the pulmonary resistance, and can the skeletal muscle ventricle eject against the high resistance?

DR NIINAMI: We did not test SMVs in this experiment against high resistance, but SMVs have functioned well in the systemic circulation in numerous other experiments.

DR WEISEL: Too bad you have not yet completed those experiments. We hope that you will report your results to us next year.

Surgical Implications of Transesophageal Echocardiography to Grade the Atheromatous Aortic Arch

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Stroke is an especially serious complication of cardiopulmonary bypass with an incidence of 2% to 5%. This prospective study used transesophageal echocardiography (TEE) in 97 patients more than 65 years of age (mean age, 73 years) to identify those at high risk for aortic atheroemboli. The atheromatous disease of the aorta was graded by TEE: grade I = minimal intimal thickening (n = 29); II = extensive intimal thickening (n = 33); III = sessile atheroma (n = 15); IV = protruding atheroma (n = 10); V = mobile atheroma (n = 10). Clinical evaluation was also performed by intraoperative aortic palpation. Four patients who were graded as having normal aortas by palpation had intraoperative strokes. In contrast, 3 of these 4 patients were in grade V on TEE. The relationship of TEE to incidence of stroke was statistically significant ($p < 0.006$), whereas there was no significant correlation between clinical grade and stroke incidence. Four of 10 TEE grade V patients were treated with hypothermic circulatory arrest and aortic arch debridement, and none suffered strokes. The other 6 patients were treated with standard techniques, and 3 had strokes. These results suggest that patients with mobile atheromatous disease are at high risk for embolic strokes that are not predicted by routine clinical evaluation. Selective use of circulatory arrest in the presence of TEE-detected mobile arch atheromas may reduce the risk of intraoperative stroke.

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Stroke is an especially serious complication of cardiopulmonary bypass with an incidence ranging from 2% to 5% and always in excess of 1% in various reports [1]. The incidence of this complication increases in patients more than 70 years of age, with stroke rates rising to as high as 7% [2]. Obvious potential causes include air embolism, particulate matter from the heart-lung machine, embolization of thrombotic or calcific material from the heart, and associated carotid artery disease. All too often, however, the exact cause is unknown.

For several years an unusually high incidence of stroke has been associated with cardiopulmonary bypass in patients with calcific atherosclerotic disease in the ascending and transverse aorta. Apparently, emboli can result from such atheromatous ulcers, similar to emboli that arise from atheromatous lesions located at the carotid bifurcation. This problem has been studied clinically at New York University for several years. In 1986 a short report described a long arterial arch cannula that was routinely used in older patients [3]. The tip of the cannula is placed beyond the orifice of the left subclavian artery in an attempt to avoid embolization to the head from the undersurface of the arch. Also, a technique of aortic arch debridement under deep hypothermia was briefly described and has been intermittently applied since that time [3].

These earlier studies, however, were hampered by the inability to diagnose intimal ulcerations within the transverse aortic arch and complicated by the fact that unnecessary arch exploration is associated with a certain inherent morbidity. The recent development of intraoperative transesophageal echocardiography (TEE) has provided a diagnostic method for recognizing such atheromatous aortic arch disease. The present study describes an attempt to evaluate the usefulness of TEE for detection and consequent special treatment of atheromatous aortic arch disease during open heart operations in an elderly population.

Material and Methods

The study group comprised 97 patients over the age of 65 years (mean age, 73 years; range, 65 to 87 years) who underwent open heart operations from August 1990 to January 1991. There were 59 men and 38 women. In this prospective, nonrandomized study, effort was made to evaluate all patients in this age group who underwent a

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cardiac operation during this time period. However, the patients were not consecutive due to problems of equipment availability. Fifty-three (54.6%) patients underwent coronary artery bypass grafting, 14 (14.4%) aortic valve replacement and coronary artery bypass grafting, 10 (10.3%) mitral valve replacement and coronary artery bypass grafting, 6 (6.2%) aortic valve replacement, 6 (6.2%) mitral valve replacement, 6 (6.2%) multiple valve replacement, and 2 (2.21%) repair of left ventricular aneurysm and coronary artery bypass grafting.

After induction of anesthesia and intubation of each patient in the study, a TEE probe was placed. After median sternotomy, the ascending aorta and transverse arch were carefully palpated and classified into three grades based on the degree of atherosclerotic disease noted: normal to mild, moderate, or severe. Transesophageal echocardiography of the transverse arch of the aorta (as well as the ascending aorta in cases where the biplane probe was used) was performed and recorded using the Hewlett-Packard single plane 5-MHz TEE or the ATL Biplane 5-MHz TEE probes and the Hewlett-Packard 500K color flow Doppler system or the ATL ultra Mark-6 color flow Doppler system. The degree of atherosclerosis present was classified into one of five grades using the criteria described by Katz (unpublished). These five grades are as follows: I = no disease or minimal intimal thickening, II = extensive intimal thickening, III = sessile atheroma, IV = protruding atheroma, and V = mobile atheroma in the lumen.

The echocardiographic findings were then compared with the findings on palpation by the operating surgeon, who then decided whether to modify the planned operative procedure or not. In all cases palpation was used to assess the aorta and to avoid cannulation through areas of calcification. The first major decision based on TEE findings was exact placement of the long aortic arch cannula. Data from TEE were used to plan the entry point beyond the atheromatous disease if at all possible or to define the need for femoral artery cannulation. The most important decision was whether to employ hypothermia and circulatory arrest to permit aortic arch exploration before proceeding with bypass. If a neurologic deficit occurred after the operation, a neurological consultation was obtained and a computed tomographic scan of the head performed.

Circulatory arrest with aortic arch debridement was performed in 4 patients with mobile atheromatous plaques (grade V). The patients were cannulated either in the femoral artery or in the aortic arch distal to the left carotid artery. Cardiopulmonary bypass was then established and the patients cooled over a period of 15 to 25 minutes to a tympanic membrane temperature less than 20°C. In addition, their heads were packed in ice and 1 g of Solu-Medrol (methylprednisolone sodium succinate; Upjohn, Kalamazoo, MI) was given. When the period of circulatory arrest was started, cold blood potassium cardioplegia was given retrograde through the coronary sinus to completely arrest the heart, usually injecting 15 to 20 mL/kg at a rate of about 150 to 200 mL/min.

Initially the patients were placed in the head-down position after which a longitudinal incision, 3 to 5 cm in length, was made in the distal ascending aorta and extended into the aortic arch. The pathologic findings were impressive. Friable, shaggy atherosclerotic material, easily dislodged on manipulation, was promptly seen bulging into the lumen. These areas corresponded to the abnormalities seen as mobile atheromas on the TEE. Initially, a metal suction line was used with the tip removed to perform a "suction endarterectomy" of loose material. Once the material was removed, an ulceration was found in the aortic intima, often more than 1 cm in diameter. Rongeurs were used to remove any loose plaques at the edges, but extensive endarterectomy was not performed. The entire ascending aorta and arch were then copiously irrigated and the aortotomy was then sutured with continuous 4-0 or 5-0 Prolene (Ethicon, Somerville, NJ). As the closure was completed, cardiopulmonary bypass was restarted at a low flow rate to displace air from the aorta. Then a cross-clamp was applied and bypass was increased to a full flow rate. The period of circulatory arrest lasted an average of about 10 minutes, ranging from 3 to 15 minutes. Cardioplegia was reinfused at this time, the patient rewarmed, and the operation performed.

Statistical analyses were performed using the χ^2 and Fisher's exact tests.

Table 1. TEE Grades and Clinical Grades of the 4 Patients With Intraoperative Strokes

Patient No.	Clinical Grade	TEE Grade
1	Mild	V
2	Mild	I
3	Mild	V
4	Mild	V

TEE = transesophageal echocardiographic.

Results

Four among the 97 patients (4.1%) had an intraoperative stroke. The mean age of 74 years in the group with stroke was not significantly different from that of the group without stroke. The sex and type of operation also did not correlate with the incidence of stroke. Four sets of variables were analyzed in detail: abnormalities detected on palpation and the relationship to incidence of stroke, findings on TEE and the relationship to incidence of stroke, comparison of findings on palpation with the degree of atheromatous disease in the aortic lumen, and efficacy of aortic debridement with hypothermia and circulatory arrest.

Palpation

Findings on palpation were graded as normal or mild in 76 patients (78.4%), moderate in 13 (13.4%), and severe in 8 (8.2%). All 4 patients with intraoperative strokes fell into the normal to mild category (Table 1). There was no significant relationship between the incidence of stroke and findings on palpation.

Transesophageal Echocardiography

The severity of atheromatous disease of the aorta as graded by TEE was as follows: 29 patients (29.9%) had normal to minimal disease (grade I), 33 (34%) were considered to be in grade II, 15 (15.5%) were in grade III, 10 (10.3%) were in grade IV, and 10 (10.3%) were in grade V. As described earlier, grades IV and V represent the most severe disease, with grade V representing atheromatous disease that both projects into the lumen and has mobile components. Table 1 reveals that 3 of the 4 patients with strokes were in TEE grade V. Analysis by χ^2 test showed that TEE grade correlated significantly with incidence of stroke ($p < 0.006$). Table 2 shows the risk of stroke in each TEE grade. Of 10 patients in grade V, 3 (30%) suffered intraoperative strokes. Of the remaining 87 patients, only 1 (1.1%) had a stroke ($p = 0.005$).

Relationship of Palpation to Transesophageal Echocardiographic Grade

Seventy-six patients had normal aortas by palpation. Sixteen of these patients (21%) were graded as having severe disease on TEE (IV or V) (Table 3). Eight patients were clinically graded as having severe disease, but only 2 of these (25%) were in TEE grades IV or V. Twenty patients were graded as having severe disease (IV or V) on TEE. However, 16 (80%) of these were judged to have normal aortas by palpation (Table 4). Obviously, the correlation between clinical grade and intraluminal disease on TEE was weak.

Efficacy of Circulatory Arrest and Aortic Debridement

Ten patients had mobile atheromatous plaques (grade V). Four patients underwent hypothermic circulatory arrest with aortic arch debridement as described, and 6 were treated with more standard operative approaches. Although no strokes occurred in the 4 patients undergoing aortic arch debridement and three strokes occurred in the 6 patients who did not have aortic debridement, the numbers are too small to achieve statistical significance.

Comment

Neurologic complications in the perioperative period of cardiac operations are associated with numerous causes. These include air emboli, particulate emboli from ventricular thrombus or valvular calcifications, carotid artery disease, postoperative cardiac arrest, and atheroemboli from diseased aortas [1]. Stroke rate has also increased with the increasing age of the operative population. Gardner and associates [2] reported that the stroke rate increased from 0.57% in 1979 to 2.4% in 1983, whereas mortality diminished over the same period of time. The incidence of stroke was as low as 0.42% for patients 40 to 50 years of age and as high as 7.14% for patients older than 75 years. Stoney and co-workers [4] reported that neurological complications arising in association with a diseased aorta was one of the primary factors causing unexpected death after cardiac operations.

Embolization of atherosclerotic debris from the aorta during a heart operation may be caused by cannulation, construction of proximal anastomoses, and cross-clamping of diseased aortic areas. Even simple palpation of the calcified aorta has been implicated as a cause of stroke [3]. There are numerous surgical techniques for diminishing the risk of stroke associated with the atherosclerotic aorta. Most techniques concentrate on minimizing direct handling of the aorta, and certainly these maneuvers are important. These techniques include distal arch cannulation with a long cannula [3], placement of the arterial cannula in alternative sites such as the femoral or axillary artery, coronary bypass with fibrillation and no cross-clamping [5], alternative sites for placement of proximal anastomoses such as the innominate artery or the internal mammary artery [3], and use of only arterial bypass grafts such as both mammary arteries and the gastroepiploic artery to avoid the necessity of attaching any graft to the diseased aorta [6]. For the severely calcified aorta, aortic arch exploration and debridement has been described [3].

None of these techniques, however, has eliminated the occurrence of stroke. The main unsolved problem is

Table 2. Risk of Stroke Versus Transesophageal Echocardiographic Grade

Grade	Incidence of Stroke	Percent
I	1/29	3.4
II	0/33	0
III	0/15	0
IV	0/10	0
V	3/10	30

Table 3. TEE Grade of Patients Clinically Graded as Having Mild Disease (n = 76)

TEE Grade	No. of Patients	Percent
I	27	35.5
II	26	34.2
III	7	9.2
IV	9	11.8
V	7	9.2

TEE = transesophageal echocardiographic.

Table 4. Clinical Grade of Patients in Transesophageal Echocardiographic Grades IV and V

Clinical Grade	No. of Patients	Percent
Mild	16	80
Moderate	2	10
Severe	2	10

identification of the patient to whom a special technique should be applied. Usually this decision has been made by palpation, which has been shown to be at times both potentially dangerous and inaccurate [7–9]. In this study, extent of disease by palpation correlated very poorly with incidence of stroke, although in all cases palpation was used as a guide to avoid clamping or dislodging calcified areas. Palpation clearly did not correlate well with the extent of intraluminal disease based on TEE and was inaccurate compared with TEE in identifying a potentially serious source of emboli.

Intraoperative echocardiography directly on the ascending aorta using a hand-held probe has been used to identify high-risk patients [7–9]. This technique, however, has the disadvantage that it cannot accurately characterize the transverse arch, in which a large proportion of the pathology exists.

In this study, TEE seems to be a safe and reliable technique to evaluate atherosclerotic disease of the transverse arch. The severity and type of the disease found (TEE grade V) correlated strongly with the incidence of stroke. Three of the four strokes that occurred were in patients in TEE grade V. Only 1 patient suffered an intraoperative neurologic event in grades I through IV. This occurred in a patient undergoing coronary artery bypass with concomitant aortic valve replacement who appeared to have normal aorta both on palpation and TEE. However, the aortic valve was severely calcified and required extensive debridement. The patient had a small internal capsule infarct on computed tomographic scan and was discharged without a neurologic deficit. This suggests that the stroke may have resulted from a calcific embolus from the diseased valve. These data indicate that TEE can successfully identify and categorize patients as either low or high risk for stroke associated with aortic plaque.

In some institutions where intraoperative TEE may not be available, preoperative TEE could be used as an alternative means of evaluating aortic disease. Although this approach has the potential to exacerbate symptoms in patients with ischemic heart disease, such preoperative exacerbation has rarely occurred in the extensive experience of our institution's echocardiographic laboratory.

After identification of patients at high risk for aortic atheroemboli, the most important question remains. Does modification of operative techniques based on these findings result in lower risk of neurologic events? The New York University group has previously reported exploration of the aorta and arch debridement in 12 patients with severely calcified aortas. All patients recovered without neurologic deficit, but the indications for arch exploration remained ill-defined. In the present study 10 patients had mobile atheromatous plaques on TEE, identifying these as the patients at highest risk for stroke. The surgeon elected to treat 4 patients in this group by hypothermic circulatory arrest and aortic arch debridement. All 4 recovered uneventfully and without neurologic deficit. The remaining 6 patients were treated with more standard approaches to the diseased aorta, and 3 (50%) had strokes. Although the difference between these two groups is not statistically significant owing to small sample size, the good results in identifying patients for arch debridement is encouraging. Clearly, the overall efficacy of aortic debridement as a mode of treatment remains to be determined based on larger numbers of patients.

Less extensive modifications in surgical technique may be appropriate in some circumstances. Grade IV lesions and distal grade V lesions may simply require changing the type of cannula or cannulation site. A soft arch-type cannula can be placed with its tip distal to the left subclavian artery to avoid showering emboli to the arch vessels. Transesophageal echocardiography can also be used to locate areas without disease for use as the cannulation site.

In conclusion, one of the most hazardous groups of patients in heart surgery are those with clinically normal aortas by palpation but extensive atherosclerotic disease of the intima. Transesophageal echocardiography can safely and reliably identify this population, while separately identifying the population at low risk for atheroemboli. Standard techniques can be applied to the low-risk patients with a relatively low risk of stroke. In contrast, patients found to have mobile atheromatous plaques of the ascending aorta and proximal arch are at high risk for intraoperative strokes and may benefit from hypothermic circulatory arrest and arch debridement. However, studies in larger numbers of patients or randomized trials may be required to determine if this technique can significantly reduce the number of atheroembolic strokes.

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DISCUSSION

DR DELOS M. COSGROVE III (Cleveland, OH): I think that this report has brought to us a very important problem which is clearly emerging as we move into the period of operating on older and older patients. I think that this will help us better define the origin of strokes and other embolic problems in the future.

DR NICHOLAS T. KOUCHOUKOS (St. Louis, MO): Dr Ribakove and his associates have focused on a problem that is becoming more and more important as the mean age of the patients who undergo cardiac operations continues to increase. We have taken a slightly different approach to the detection and management of severe atheromatous disease of the ascending aorta and the proximal aortic arch.

We use a 7-MHz transducer, which is applied directly to the ascending aorta, and have not relied on transesophageal echocardiography. This method can also be used to evaluate the proximal arch. We have examined 331 consecutive patients with this technique, all of whom were over the age of 60 years. Atherosclerotic disease that we deemed severe enough to warrant a change in the operative technique was found in 14% of the patients, and in 2.5% of the patients, or 8 of the total, it was so extensive that we substantially modified the procedure, using femoral cannulation, total circulatory arrest, and replacement of a segment of the ascending aorta and the proximal arch.

Several scans of the aorta are shown on this slide (slides not reproduced). The two on the left show an essentially normal aorta, and those on the right show serious calcification posteriorly and marked thickening of the anterior portion of the aorta. The upper panel is a transverse view and the lower panel is a longitudinal view.

This aorta has severe atherosclerotic disease, and I believe it would correspond to the grade IV classification of Dr Ribakove and his colleagues. All of the disease is located anteriorly. We elected to use total circulatory arrest in this patient with replacement of the aorta. This slide shows the longitudinal view with atheromatous material projecting into the lumen.

This slide shows the segment of aorta that was removed and the marked atheromatous changes.

We agree with Ribakove and associates that evaluation of the aorta by the conventional methods of inspection and palpation clearly do not correlate with what is seen by ultrasonography and on gross examination of the aorta. Use of intraoperative ultrasonography, whether one uses the surface probe or the transesophageal approach, may reduce the incidence of stroke that is related to embolization of atherosclerotic material.

Dr Ribakove, do you believe that transesophageal echocardiography can detect atheromatous disease in the ascending aorta or in the proximal arch, where placement of clamps and cannulas can be associated with embolization of atherosclerotic material?

DR RIBAKOVE: I would like to thank Dr Kouchoukos for discussing this. Obviously his group has done some very important work on this topic. Approximately 20% of the cases in this study were done by biplane transesophageal echocardiographic probe, which has the ability of looking at the ascending aorta very well. I think the advantage of the transesophageal probe is that you get an excellent look at the entire arch, which is something that is very difficult to do in many of the cases when you are using a hand-held probe. There are other advantages as well, not having to run the risk of breaking sterile technique and allowing the surgeon to continue operating as the echocardiography is being done.

DR WILLIAM C. NUGENT (Hanover, NH): We are great advocates of the transesophageal probe but have been less consistent in getting high-quality visualization of the entire arch. It is excellent for the ascending and excellent for the proximal descending arch, but we have had less success getting consistent views of the transverse arch. I am curious to know, did you follow up any of the patients with grade IV disease to find out if some of these mobile plaques were in fact gone after the procedure when they subsequently woke up with their strokes, or have you found any way of correlating findings after cross-clamping with transesophageal echocardiography with postoperative status?

DR RIBAKOVE: Well, just to correct, for our grading system the mobile atheromatous plaques were grade V. There was actually a case early in the study when one of these mobile atheromatous plaques was seen on transesophageal echocardiography and the surgeon chose to use a standard approach to the operation. After bypass the mobile plaque was no longer there and the patient had a serious stroke.

DR G. FRANK O. TYERS (Vancouver, BC): You described the intraoperative use of transesophageal echocardiography, but I am curious as to why you just would not do this preoperatively so that you could plan your approach to the arch.

DR RIBAKOVE: There are two reasons. That is actually a good point. It certainly can be done preoperatively, and you can use the information in the operating room. One potential disadvantage of doing it preoperatively is that many of these patients are seriously ischemic and there is the possibility of exacerbating their symptoms during transesophageal echocardiography. However, in our echocardiography laboratory that has not been a problem. So certainly I think for hospitals that do not have intraoperative echocardiography available, preoperative echocardiography can be helpful.

There is one major advantage of doing this intraoperatively. Localization of these mobile plaques by the echocardiographer in conjunction with palpation by the surgeon is more accurate intraoperatively. This allows the surgeon to avoid the most diseased portions of the aorta.

DR COSGROVE: Could I ask two questions? Who do you recommend have studies, everybody over the age of 60 years? And second, having seen these sessile plaques, do you persist in using a long cannula to try to go past the head vessels?

DR RIBAKOVE: In response to the first question, we actually are not at the point, I think, based on these data, where we should recommend any patients must have this. It appears to be a helpful technique, but I think that a lot more data should be available before we are caught in the trap of saying that any patient must have intraoperative transesophageal echocardiography. We think it will be helpful in the elderly population; we used it in patients over the age of 65 years. We think it will also be helpful in those patients who are at high risk for aortic atherosclerosis, and possibly those patients with severe peripheral vascular disease. Your second question?

DR COSGROVE: Do you still use the long tip on your aortic perfusion cannula?

DR RIBAKOVE: Yes. It is not actually done routinely. It depends on the patient. Before this study most of us were using it for patients who had palpable, calcific, atherosclerotic disease of the aorta. Some members of our faculty were using it for all patients over the age of 65 years. It is now being used for both of those reasons, and in addition, when a patient is seen to have atheromatous disease that is more proximal, we use the long tips to reach past the left subclavian artery.

DR COSGROVE: Dr Kouchoukos, I know that you now have had a large experience with this. What do you recommend as far as what we do and who we study?

DR KOUCHOUKOS: We are presently evaluating a larger cohort of 500 patients to determine the risk factors that correlate with the presence of serious atherosclerotic disease in the ascending aorta. From our preliminary analysis, it appears that diabetes, severe peripheral vascular disease, carotid artery disease, and left main coronary disease are the major predictors of the presence of severe atheromatous disease in the aorta.

Dr Ribakove raised the issue of sterility with the surface probe. In more than 500 patients, we have not had a complication that we could attribute to the probe. It can be easily and safely applied to the ascending aorta using a sterile bag.

DR COSGROVE: Lest the magnitude of this problem be lost on some of us, in 1989, 30% of the patients who were autopsied at the Cleveland Clinic had evidence of peripheral atheroemboli, and if we are seeing this amount, I imagine that there must be at least that much more that we are not seeing. This is a very serious problem, and I think we have heard today a potential use for echocardiography to help us make that diagnosis preoperatively.

The Carpentier-Edwards Pericardial Aortic Valve: Intermediate Results

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The Edwards pericardial aortic valve has unique design features that minimize cusp stress and reduce abrasion wear. Wear tests and in vivo fluid dynamic tests have shown superior performance compared with other bioprostheses. Between August 1981 and July 1985, 719 isolated aortic valves were implanted in 10 US centers. Patients were aged 18 to 90 years (mean, 64 years). Men were 63.3% of the patients. Aortic stenosis was present preoperatively in 63.4% of patients. New York Heart Association functional classes III and IV were assigned to 62% of the patients. Valve sizes were 21 mm or less in 49% of patients. Concomitant procedures (most often coronary artery bypass grafting) were performed in 48% of patients. Hospital mortality was 4.7%. There was one valve-related death due to anticoagulant hemorrhage. Late mortality yielded 23 valve-related deaths: endocarditis (13), anticoagulant hemorrhage (4), thromboembolism (3), structural (2), and pannus overgrowth (1). Freedom from valve-related death at 7 years was 95.5%. Regarding valve survival, cusp tears were not seen. There were 11 calcified valves and eight explants (57 to 107 months). Seven-year freedom from all valve reoperation was 95.5%, with 11% of the patients receiving warfarin sodium, freedom of the total series from hemorrhage at 7 years was 93.3%, and from major thromboembolism, 95.8%. Echocardiographic follow-up of hemodynamics at 7 years yielded the following calculated effective orifice areas: 19 mm, 1 cm^2; 21 mm, 1.3 cm^2; and 23 mm, 1.4 cm^2. Average mean gradient for 19-mm valves was 15 mm Hg. New York Heart Association class improved in 78% of the patients. The Carpentier-Edwards pericardial valve, carefully studied by the Food and Drug Administration guidelines, is easy to use and has excellent hemodynamics. At 7-year follow-up there were no cusp tears and very little calcification. Intermediate-term performance is as good as or better than that of currently available devices, thus making this valve an outstanding bioprosthesis for the small aortic root.

(Ann Thorac Surg 1992;53:764–71)

The Carpentier-Edwards (Baxter Healthcare Corporation, Edwards CVS Division, Irvine, CA) glutaraldehyde-tanned pericardial xenograft aortic valve (model 2700) was shown early to have the excellent hemodynamics characteristic of this type of valve [1]. This was achieved with a design that had adjacent pericardial cusps being passed between the two limbs of a wire form stent rather than being wrapped around a post. This feature, together with computer aided cusp and stent design, resulted in excellent wear testing performance compared with other bioprostheses [2]. This promise of improved performance led us and some other surgeons to conduct a clinical trial of its use.

Material and Methods

The Valve

The skeleton of the Carpentier-Edwards Aortic Model 2700 valve is a flexible corrosion-resistant nonmagnetic alloy wire formed into a three-pronged scalloped shape. Each prong has two parallel wires leading up to a rounded apex. The essential difference between this and other three-leaflet pericardial valves is that the two pieces of pericardium of adjacent cusps pass between the two limbs of the wire form prong, rather than around the stent or prong.

The shape of the pericardial cusps and the wire form were determined with the aid of finite-element analysis. Their thicknesses are carefully chosen to match each size of valve. Analysis shows stress to be maximal at the free edge near the top of the posts. In the body of the cusp stresses are somewhat higher around the perimeter and in the belly. All trileaflet valves have similar distributions of stress, but good design can minimize this.

The stent flexes and rebounds with moderate finger pressure. The cusps have a small gap at their central meeting point, which in natural valves is filled by the corpora arantii. This gap is seen to be obliterated during closure at normal diastolic pressure in the pulse duplicator. Moderate distortion does not render the valve grossly incompetent. This does not of course, free the surgeon from the obligation to match valve and annular size and place the sutures so as to avoid distortion. Fixation of the

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Table 1. Isolated Aortic Valve Implants

Principal Investigator	Institution	No. of Implants (%)
Denton Cooley, MD	Texas Heart Institute	14 (2.0)
Delos M. Cosgrove III, MD	Cleveland Clinic Foundation	272 (37.0)
Robert W. M. Frater, MD	Montefiore Hospital	88 (12.2)
Robert W. M. Frater, MD	Albert Einstein Hospital	86 (12.0)
Donald Magillian, MD	Henry Ford Hospital	44 (6.1)
Shabudin Rahimtolla, MD	Univ. of Southern California	25 (3.5)
W. Gerald Rainer, MD	St. Joseph Hospital	48 (6.7)
W. Gerald Rainer, MD	Presbyterian/St. Luke's Hospital	18 (2.5)
Neal W. Salomon, MD	Good Samaritan Hospital	113 (15.7)
George Zorn, MD	University of Alabama	11 (1.5)
Total		719 (100.0)

pericardium is by standard glutaraldehyde tanning methods.

Conditions of Implantation

At all institutions participating in the trial, the study plan and the informed consent form were approved by the local Investigational Review Board. The participating surgeons undertook to aid in the careful and complete follow-up of the patients.

Patient Inclusions and Exclusions

All patients with isolated aortic valve replacements were included. Patients undergoing multiple valve operations were excluded. There were no exclusions for other concomitant operations (eg, coronary artery bypass) or for age, sex, size, severity of disease, pathology, race, or economic status.

Study Centers and Distribution of Patients

There were ten reporting hospitals. Valves were available for implantation between August 1981 and July 1985, and 719 isolated aortic valve replacements were performed during this time (Table 1). The names of the surgeons locally responsible for the study are given. Other surgeons in each institution were also responsible for implantations.

Follow-Up

The follow-up information was gathered by physician assessment for the first postoperative year at discharge, 30 days, 6 months, and 1 year. After 1 year the patient was assessed annually by direct contact with the patient or the patient's physician. The clinical data presented represent follow-up ending April 1990. The number of postoperative patient years is 3428.68 with a mean follow-up of 4.8 years. In the latest update of the 550 eligible patients, ie, patients not known from previous surveys to have died or been removed for cause, 496 were contacted.

The loss of 10% of the patients over the course of the study is related to the presence in the original group of poor inner-city patients whose nomadic lifestyle results in great difficulties with long-term follow-up.

The subjective areas of follow-up such as the symptomatic status according to the New York Heart Association system and the occurrence of transient ischemic attacks were evaluated by the asking of specific questions. Late assessment of valvular performance and structural change was made largely by two-dimensional echocardiography. In 1981, when the study was started, echocardiography was not accepted by the Food and Drug Administration (FDA) as a method of follow-up. There were limited requirements for postoperative catheterization, but even these proved impossible to achieve in the US, and 2 years ago the FDA finally made echocardiography a legitimate method of valvular monitoring. Because entry to the study started in 1981 and ceased in 1985, echocardiography was never a formal part of the protocol. It is, however, being used in more and more of the long-term patients, and in 1989, 25% of the patients received echocardiographic examination. Cardiac catheterization was performed for cause rather than for follow-up purposes. Anticoagulation therapy was at the discretion of the patient's physicians.

Mortality and Morbidity

The guidelines for reporting morbidity and mortality after cardiac valvular operations [3] have been observed in the preparation of this report.

All artificial valves are mildly stenotic and have some insufficiency in closing. Modern echocardiography is sensitive enough to show this level of difference from the normal natural valve. In clinical studies there is inevitably a scatter of data with some valves being more obstructive or leaking somewhat more than others, even though none has hemodynamically significant levels of stenosis or insufficiency. In addition to this variation in anatomically normal valves it also happens that, with time, some bioprosthetic valves have thickening of one or more cusps. This may be present for years without resulting in any detectable hemodynamic change. Although the Guidelines use the terms *deterioration* and *change*, this implies the recording of multiple observations over time. It seems reasonable to separate results of postoperative clinical echocardiographic and cardiac catheterization observations into several groups: (1) structural change meriting reoperation, (2) structural change without indication for reoperation, and (3) patient-valve mismatch with abnormal hemodynamics due to the insertion of too small a valve for the patient's normal cardiac output.

Statistical Analysis

The postoperative data are divided into two periods. The operative period includes all complications occurring in the first 30 days after operation. This was the standard used at the start of the study in 1981.

The postoperative period includes all complications occurring more than 30 days after operation. Linearized rates, expressed as percent per patient year (%/pty), reflect all complications occurring in the postoperative period (>30 days). Actuarial analyses for survival and valve-related complications are expressed as percent event-free (standard error) at 7 years and include all events in both the operative (≤30 days) and postoperative (>30 days) periods. The actuarial life-table method of Cutler and Ederer was used. The statistical analyses of these data were performed by the biostatisticians at Baxter Edwards CVS Division. The term *eligible patients* refers to all patients not known to be dead or to have had a reoperation at the time of the survey. Some of these eligible patients have in fact already been lost to follow-up.

Results

Patients

The ages of the 719 patients ranged from 18 to 90 years with a mean at implantation of 64 ± 12.4 years. Men were 63.3% of the group. The New York Heart Association classification before operation of the patients followed up in 1989 and their current status are given in Table 2. More than 60% were in class III and IV preoperatively, but aortic stenosis patients with typically moderate symptoms constituted a substantial part of the group. In 1989, 78% showed improvement and 12% no change, 2% a worse status with 10% unknown, and 7% were dead. The pathology of the explanted valves is given in Table 3, and the sizes of implanted valves in Table 4.

Surgical Mortality

Thirty-four patients died in the 30-day operative period, giving a mortality of 4.7%. The one valve-related death resulted from a warfarin sodium (Coumadin, Du Pont Pharmaceuticals, Wilmington, DE)-related hemorrhage.

Hemodynamics

For completeness' sake hemodynamic data on effective orifice areas previously reported on these patients are included here (Table 5) [1, 4–7]. The intraoperative hemodynamic studies were conducted using simultaneous direct left ventricular and aortic pressure and cardiac output measurements. The echocardiographic valve studies at the Weiler Division of Montefiore Hospital were done between the first and fifth years after operation. All valves were structurally normal at the time of study. The studies performed at the Good Samaritan Hospital were done at a mean follow-up of 67 months (range, 49 to 86 months) (Fig 1).

Table 2. New York Heart Association Class

Class	Preoperative	Postoperative
I	26	354
II	130	103
III	232	12
IV	66	3

Table 3. Pathology of Explanted Valves

Pathology	Number	Percent
Stenosis	456	63.4
Regurgitation	117	16.3
Mixed disease	110	15.3
Dysfunctional prosthetic valve	36	5.0

Thromboembolism

Thromboembolic events were reported in 74 patients. Three patients had peripheral emboli (2 requiring operative removal), and 66 patients had central nervous system emboli, 46 being transient ischemic attacks and 20 leaving residua. Three of the latter patients died of the effects of the emboli.

Twenty-three patients experienced emboli during the hospitalization or within the first 30 postoperative days. Five of these patients were taking Coumadin and 2, antiplatelet agents. Of the 51 patients experiencing emboli from 30 days onward, 1 was receiving Coumadin (3 with dipyridamole), and 13, antiplatelet agents.

Of the total patient population 11% were being treated with Coumadin (with or without dipyridamole), 26% with aspirin, and 17% with aspirin and dipyridamole.

The linearized rate of embolism was 1.66%/pty, and the actuarial event-free rate for all kinds of thromboembolic incidents at 7 years was 86.25%. For incidents leading to death or residual morbidity the event-free rate at 7 years was 94.17% (0.01%) (Fig 2).

Anticoagulant Therapy and Hemorrhage

There were 30 anticoagulant-related hemorrhages meeting the definition of the guidelines. Ten occurred during the first 30 days. Nine of these patients were receiving Coumadin, and 1 died. Twenty hemorrhages occurred during the postoperative period. Fifteen of these patients were receiving Coumadin (three fatalities) and 2, Coumadin and dipyridamole (1 fatality). Three episodes occurred in patients given antiplatelet therapy without fatality. The linearized rate of occurrence was 0.88%/pty, and the hemorrhagic complication event-free rate at 7 years was 93.3% (0.01%).

Endocarditis

All 27 cases of bioprosthetic infection occurred after 30 postoperative days for a linearized rate of 0.79%/pty and a 7-year event-free rate of 94.88% (0.01%). There were 13 deaths, three after valve replacement. One patient sur-

Table 4. Sizes of Implanted Valves

Valve Size (mm)	Percent
19	15.5
21	31.6
23	24.7
25	17.8
27	6.3
29	4.0

Table 5. Effective Valve Areas (cm²)

		Hemodynamic		Echocardiographic	
Size	In Vitro [1]	Intraop [4]	Intraop [5]	Postop [4, 6]	Postop [7]
19	. . .	. . .	. . .	1.3 (n = 4)	0.97 (n = 9)
21	1.5	1.3 (n = 3)	1.3 (n = 16)	1.5 (n = 13)	1.3 (n = 16)
23	. . .	1.5 (n = 8)	2.0 (n = 19)	1.6 (n = 13)	1.5 (n = 15)
25	2.3	2.9 (n = 6)	2.2 (n = 7)	1.8 (n = 7)	1.8 (n = 6)

vived rereplacement, and 13 patients were successfully treated medically without further recurrence.

Valve Durability, Rereplacement, and Reoperation

STRUCTURAL CHANGE. There were no valve reoperations in the 30-day operative period. Beyond 30 postoperative days, eight explants for valvular dysfunction were reported. All were for stenosis caused by valve calcification; all patients survived rereplacement. The mean implant time for calcified valves was 80 months, with a range of 57 to 107 months. The ages of the patients were from 44 to 73 years. Three other patients appear to have shown major structural change: 2 had valve areas calculated by echocardiography at less than 1 cm² and could reasonably be classified as having structural change meriting reoperation, but have thus far continued to be followed up medically, and 1 other patient has died with a valve described as calcified. It is notable that no cusp tears occurred. The event-free rate for structural valve deterioration was 97.2% at 7 years (0.32%/pty) (Fig 3).

STRUCTURAL CHANGE NOT REQUIRING REOPERATION. There were 17 of these cases. Eleven showed some stenosis and 4, insufficiency. Two were incidentally found wire fractures discovered in explanted valves, one for a perivalvular leak and one for endocarditis. It should be noted that because echocardiographic follow-up studies were not done in 100% of the patients, there will probably be patients with as yet undetected structural change not requiring reoperation.

PATIENT VALVE MISMATCH. Two large patients with size 19 valves have, by echocardiography, high gradients without structural change. They have not undergone reoperation.

NONSTRUCTURAL VALVE DYSFUNCTION. One valve was removed for insufficiency caused by massive pannus ingrowth. The patient died postoperatively. Nine patients were reported to have perivalvular leaks. One had successful repair at 22 months. One, whose initial operation was for endocarditis, had the leak repaired at 2 months. The perivalvular leak recurred, and the valve was successfully explanted and replaced at 70 months. The remaining patients have minor or insignificant leaks defined by echocardiography, and are being followed up medically. Also included under this heading, for purposes of analysis, are the 2 patients with patient-valve mismatch. The event-free rate for nonstructural change was 97.6% at 7 years (0.38%/pty) (Fig 4).

HEMOLYSIS. Hemolysis has been detected in 1 patient with stenosis and 1 with no detectable valve change and a diagnosis of "hemolytic anemia." Both are on iron therapy. One other patient, diagnosed by the investigator as having grade 2/4 insufficiency by angiography, had detectable hemolysis. The patient died 6 years postoperatively of an arrhythmia secondary to atherosclerotic heart disease.

REREPLACEMENT FOR ENDOCARDITIS. Four patients had rereplacement for endocarditis with 1 survivor.

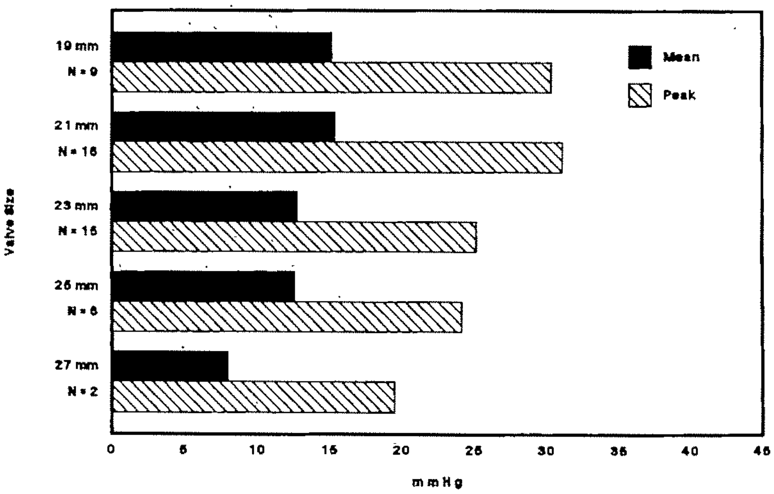
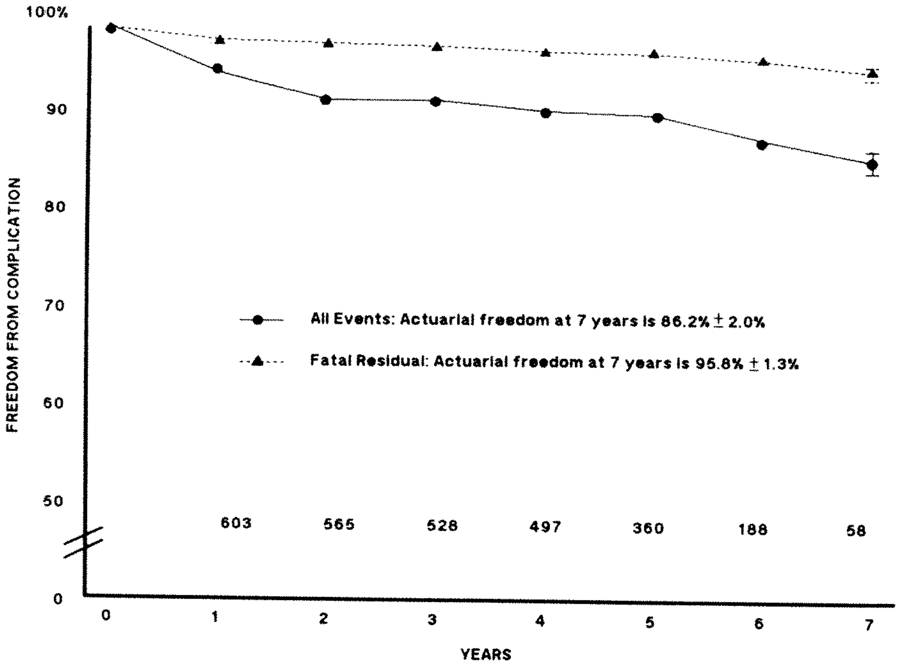


Fig 1. Transvalvular gradients obtained postoperatively by two-dimensional echocardiography at Good Samaritan Hospital.

Fig 2. *Event-free actuarial survival curve for all thromboemboli and thromboemboli with fatal or residual effects.*

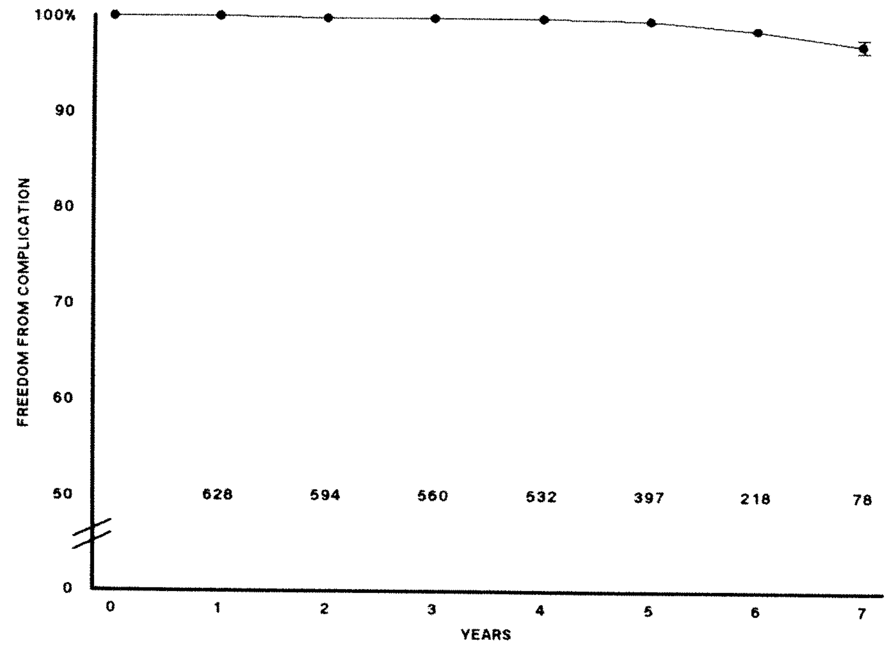


SUMMARY OF REREPLACEMENT AND REOPERATION. Fifteen patients had 16 valvular reoperations (Fig 5). There were 8 rereplacements for calcification, 4 for endocarditis, 1 for insufficiency caused by pannus overgrowth, and 1 for a failed repair of a perivalvular leak. There were two repairs of perivalvular leaks, and one successful repair was followed by rereplacement. The event-free rate for reoperation was 95.7% (0.01%) at 7 years.

Mortality

A total of 198 deaths occurred, including the patients who died in the 30-day operative period, giving a mortality of 4.7%. In the postoperative period 164 patients died (4.7%/pty). Twenty-three of these were considered as definitely valve-related (0.67%/pty): 13 were due to prosthetic valve endocarditis, 4 to Coumadin-related hemorrhage, 3 to thromboembolic events, 2 to structural valve deterioration, and 1 to nonstructural valve dysfunction. The two cases of structural deterioration resulted from stenosis (one of undefined cause and one due to calcification in a renal failure patient). The nonstructural valve dysfunction was the case of pannus ingrowth already described. In addition there were 16 patients who died of unknown causes (8 sudden) whose deaths have been included arbitrarily as valve-related, giving an incidence of 1.14%/y. Of the remaining 125 deaths, 72 were cardiac-

Fig 3. *Event-free actuarial survival curve for structural valve deterioration meriting operation. Actuarial freedom at 7 years is 97.2% ± 1.0%.*



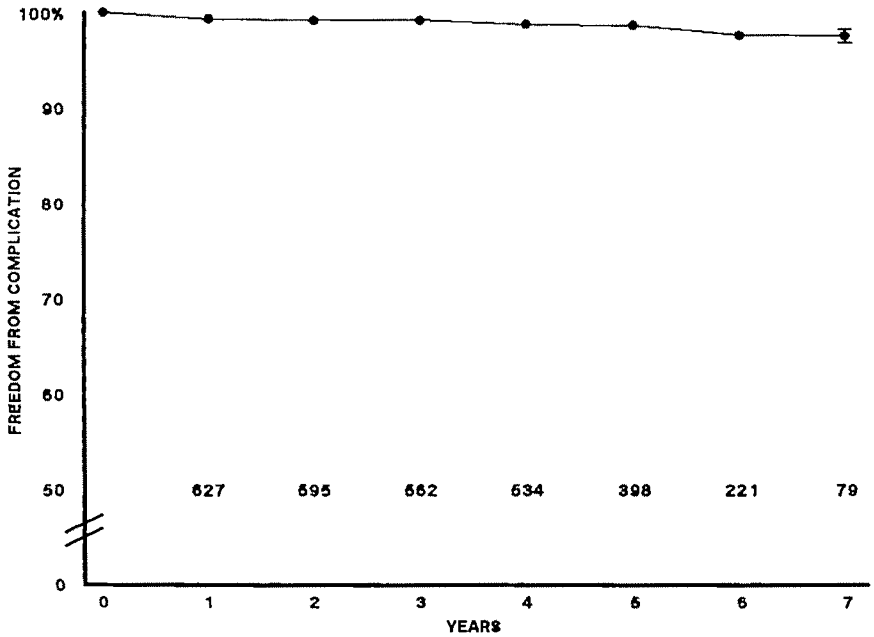


Fig 4. Event-free actuarial survival curve for nonstructural valve dysfunction. Actuarial freedom at 7 years is 97.6% ± 0.7%.

related, and 53 were due to other causes such as cancer, suicide, and leukemia. The actuarial survival rate for all causes was 67.7% (0.02%), and for valve-related causes including deaths due to unknown cause it was 92.5% (0.01%) at 7 years (Fig 6).

Comment

The model 2700 aortic pericardial valve has in this multicenter study, with a uniform and regular follow-up mandated by FDA requirements, performed very well. The 7-year actuarial event-free rates for thromboembolism, structural valve failure, endocarditis, reoperation, and valve-related mortality are all at satisfactorily low levels and quite comparable with data from series of porcine bioprosthetic aortic implantations with the same period of follow-up [8–11]. With the clearly superior hemodynamics of the model 2700, this valve then becomes a desirable choice for aortic valve replacement, especially for the small aortic root.

During the time this valve has been under trial, the Ionescu-Shiley pericardial valve was withdrawn from use and the Hancock pericardial valve was briefly introduced and withdrawn. The major problem with durability in both cases was tearing of the cusps after only a few years of use. These were largely in the mitral position, but their

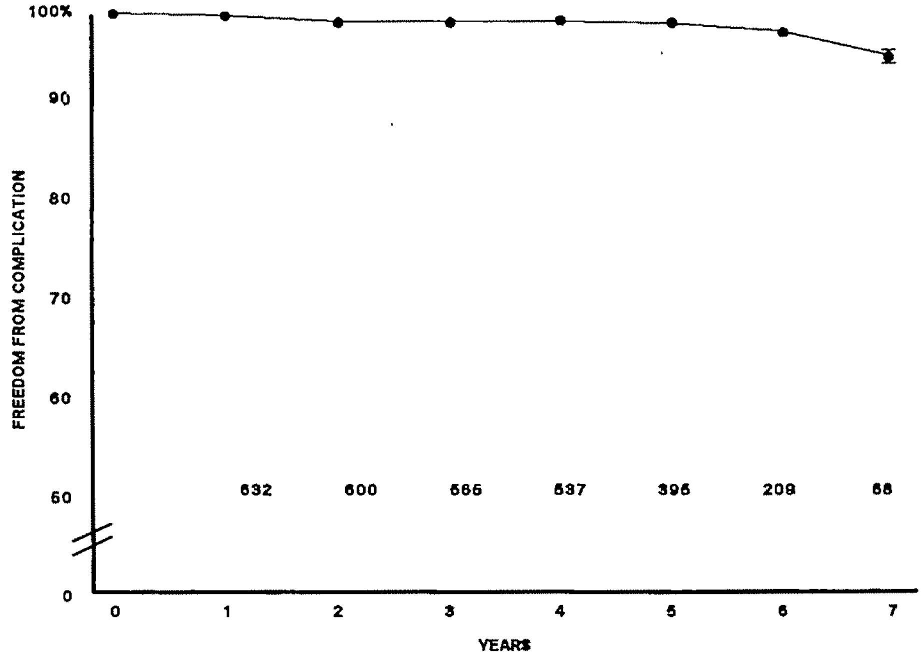


Fig 5. Event-free actuarial survival curve for valvular reoperations for all causes (intrinsic valve dysfunction, pannus overgrowth, endocarditis). Actuarial freedom at 7 years is 95.7% ± 1.4%.

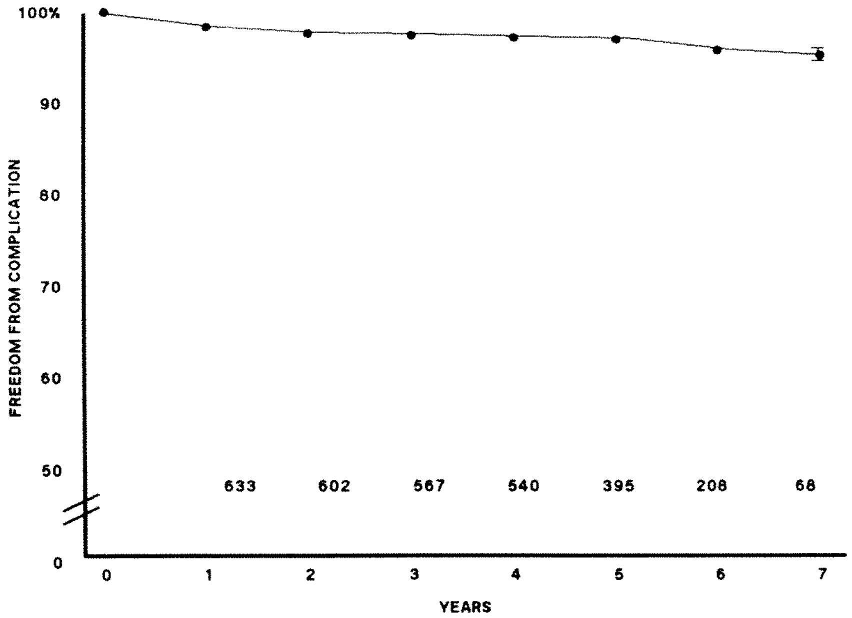


Fig 6. Event-free actuarial survival curve for valve-related mortality. Deaths due to unknown cause and sudden deaths are regarded as valve-related. Actuarial freedom at 7 years is 95.4% ± 1.1%.

occurrence led to the withdrawal from use for both the mitral and aortic positions. Wear tests defined the mechanisms of the tears: a majority were related to abrasion wear [12, 13]. Other studies defined the nature of the stress in three-leaflet valves in general and described the extra stresses in artificial valves attached to relatively immobile stents compared with those in natural valves attached to the dynamically changing aortic wall. Further studies defined the properties of natural and tanned pericardium and revealed its lack of homogeneity. All of this information leads inescapably to the conclusion that previous durability problems of pericardial valves have been related to a combination of ignorance of the particular properties of pericardium and faulty design [14–17].

The major valve-related disability in this series, and indeed also for Ionescu-Shiley valves implanted in the aortic position, has been calcification. There are no data to suggest that the development of calcification will differ in the Carpentier-Edwards pericardial valve from what occurs in porcine valves.

Finally, the nature of this trial and its implications deserve mention. The valves have been inserted and studied prospectively under a comprehensive and uniform protocol. No valves have been inserted by the US investigators since 1985. At the date of presentation in February 1991, final FDA approval for expansion of sales to the US market had not been granted. The reasons for the delay to that time appear to have had nothing to do with the results reported here. The caution displayed with this and other devices may be regarded as admirable if the only criterion is the total avoidance of potential risk. However, the failure to strike a proper balance between this, and the benefit of innovation has predictable and straightforward consequences: (1) discouragement of the innovator because of excessive delay between invention and conversion to practice; (2) enormous increases in cost purely from delay in achieving market approval; (3) inevitable increases in product price; (4) inevitable loss of market to foreign products, not necessarily any less safe than US products and certainly reaching the market more quickly and at a lower price; and (5) establishment by US valve producers of offshore manufacturing facilities. Instances of all of these have already occurred. The specter that we face is the loss of a US industry that once had total domination of the world market.

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DISCUSSION

DR W. R. E. JAMIESON (Vancouver, BC, Canada): Dr Frater and colleagues from the ten investigating centers are bringing to us today a very important communication. They have identified that pericardium, with a unique design to minimize tissue stress, can be a suitable tissue substitute for cardiac valvular prostheses. I extend appreciation to the authors for the opportunity to review the manuscript well in advance of the meeting.

We are all aware that previous pericardial designs used in the Ionescu-Shiley and Hancock pericardial valves have resulted in an unacceptable degree of structural valve deterioration in both the aortic and mitral positions. Pericardial valves have always provided superior hemodynamics but suboptimal durability. The freedom from structural valve deterioration, incorporating all potential cases in this series, is similar to that of new generation porcine bioprostheses and superior to the 82% freedom at 7 years as recently documented from the University of Ottawa with all Ionescu prostheses. Dr Frater's series, up to 7 years, is excellent.

The credit for the design must go to Dr Alain Carpentier and to the engineer-designer, Ernest Lane. The University of Montreal has also documented similar experience with the Edwards pericardial prosthesis. Calcification remains the only residual problem, and on the horizon are new chemical fixation techniques that would likely reduce this degree of failure.

I have three comments and questions for Dr Frater and associates. The use of anticoagulants in 11% of your patients has created reduced overall clinical performance, with a 93% freedom from hemorrhage at 7 years. Have you been able to compare the incidence of thromboembolism in patients receiving anticoagulants, antiplatelet therapy, and no therapy? Second, the incidence of prosthetic valve endocarditis is similar with porcine bioprostheses. In your series 13 patients survived medical therapy, but there were ten deaths that occurred without the opportunity for surgical management. And, finally, why does the regulatory process restrict United States citizens from advanced technology when marketing acceptance has been present in Canada, Asia, and Europe?

DR FRATER: I thank Dr Jamieson for his discussion. As he so clearly points out, this is a superbly designed valve for which Ernie Lane should get the bulk of the credit. The fact that this valve will calcify, I think, is certain. It is, like other bioprosthetic valves, still awaiting the final trial and approval of many anticalcification treatments now in experimental use.

Dr Jamieson asks whether the 11% Coumadin incidence made any difference to emboli: it apparently did not. The patients receiving Coumadin were not free of emboli. The numbers were not sufficient to draw statistically significant conclusions in this series to answer your question, but it is quite clear to me that an isolated aortic valve replacement with a bioprosthetic valve is not benefited by Coumadin. In this series the complication rate from Coumadin outdid any benefit that might have occurred.

The endocarditis mortality without reoperation is frustrating. It did not happen in our institution. I do not think it happened in institutions with the senior authors who were responsible for the studies. Obviously, in some institutions there was a reluctance to operate on prosthetic endocarditis. But that is an appropriate feature of a multicenter trial. We are showing you what happens with this device in the United States.

The FDA question is a really bothersome one. It is not the data presented today that is keeping this valve from use. It is a form of inertia and fear on the part of an underfunded, understaffed bureaucracy whose goal is apparently to avoid risk at all costs. The bureaucrats have, in my mind, failed to strike a proper balance between the question of risk and the benefit of innovation. And the consequences are straightforward: we are not getting valves to market. New devices are not coming to market in the United States; devices from overseas are not coming to market in the United States. Our devices run the risk of being outsold and outdesigned in other parts of the world, so that we stand a very severe risk of losing an industry in which we once dominated the world.

American companies have established offshore production facilities to avoid US regulatory difficulties, but that to me is not the right way to approach it. This is a very serious problem, and it is made more serious by the recent legislation passed in November 1990. Yet there were I think only five doctors in a conference held on this subject yesterday afternoon at 5 o'clock. We clearly do not know what is happening, and we are clearly going to miss the boat if we do not do something about it.

Successful Transplantation of Hearts Harvested 30 Minutes After Death From Exsanguination

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The donor pool for heart transplants is severely limited. Unfortunately, many trauma patients who might be donors die of exsanguination before their organs can be used. We tested whether hearts "dead" for one half hour after exsanguination could be used as heart transplants in 8 lambs (mean weight, 8 kg). Four lambs were exsanguinated by severing the subclavian artery while simultaneously infusing intravenous saline solution to mimic resuscitation attempts. All animals died. Thirty minutes after hypotensive arrest and death, simulating the time needed to secure donation permission, the heart was harvested, perfused with 250 mL of cold cardioplegia containing 200,000 units of streptokinase to dissolve intravascular clots, and stored in iced saline solution for a mean of 1.5 hours while 4 recipient lambs were prepared for operation. After bypass and recipient heart excision, the "dead" donor heart was transplanted orthotopically. The heart was reperfused with low flow (25 mL/min), low pressure (30 mm Hg), low hematocrit (hematocrit, 0.08 to 0.12) blood supplemented with prostaglandin E_1 and nifedipine for 15 minutes, followed by full flow rewarming for 45 minutes. All hearts resumed normal contractions. All animals were weaned from bypass without inotropes. Pressures a half hour after bypass were (in mm Hg): aorta, 80 ± 10; pulmonary artery, 20 ± 5; right atrium, 9 ± 5; and left atrium, 9 ± 2. We conclude that hearts "dead" for one half hour after exsanguination are capable of being reanimated and used successfully as donor organs. With further development, this method could potentially greatly expand the donor heart pool.

(Ann Thorac Surg 1992;53:772–5)

The donor pool of brain-dead patients is the principal rate-limiting step that prevents more widespread application of heart transplantation. It is estimated that, at most, only one half of potential donors are utilized due to problems with consent or failure to meet established criteria for acceptability by a particular harvest team. More importantly, there exists a much larger potential donor pool that consists principally of young adults who have died suddenly secondary to exsanguination from penetrating or blunt trauma. These victims, who prior to their precipitous demise had normal organs, might be used as donors, after obtaining appropriate consent for donation, if methods could be devised to reliably resuscitate their individual organs.

Encouraged by our initial success in "reanimating" hypoxically arrested, asystolic hearts in a lamb model, we elected to apply these concepts to a traumatic exsanguination model where factors such as intravascular coagulation and time intervals to secure permission for organ harvest might limit the concept's usefulness [1]. This report details the preliminary findings of our experimental preparation.

Material and Methods

Eight farm-raised juvenile lambs of 6 to 9 kg (mean, 8 kg) were selected as random pairs; where a size discrepancy existed, the larger of the 2 animals was chosen as the donor (Fig 1). Thus, 4 animals were to become donors, whereas the other 4 served as recipients.

The donor lambs were anesthetized with ketamine, intubated, placed on a Servo C volume ventilator and maintained on halothane anesthesia. Sixteen-gauge intravascular catheters were placed in the femoral vessels, and the arterial pressure was transduced. A median sternotomy was performed, and the right subclavian artery was dissected and looped. After stabilization, the artery was partially transected, resulting in exsanguination over a 2- to 5-minute period. Simultaneously, 500 mL of normal saline solution was administered intravenously through the femoral vein catheter to stimulate a resuscitation attempt.

Despite this fluid resuscitation, blood pressure dropped progressively over a 3- to 5-minute period until it became unobtainable. Cardiac electrical activity usually showed initial tachycardia followed by progressive bradycardia leading to cardiac standstill 5 to 14 minutes after zero blood pressure. The animal was left undisturbed for a further 30 minutes. Rectal temperatures averaged 39°C.

After the 30-minute period, simulating the time needed to secure organ donation permission, the pericardium was opened, the ascending aorta clamped, and the heart perfused with 250 mL of 4°C Roe's solution to which was

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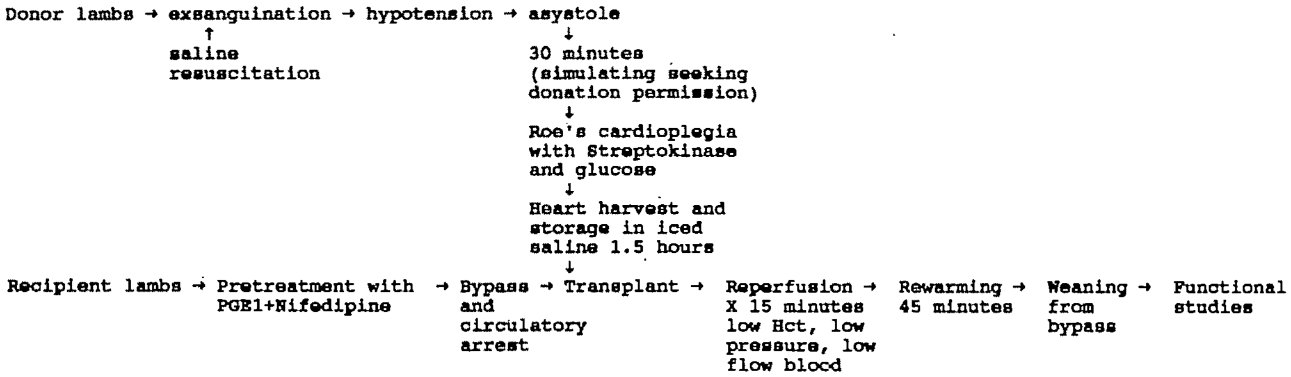
Donor lambs → exsanguination → hypotension → asystole
saline resuscitation
30 minutes (simulating seeking donation permission)
Roe's cardioplegia with Streptokinase and glucose
Heart harvest and storage in iced saline 1.5 hours
Recipient lambs → Pretreatment with PGE1+Nifedipine → Bypass and circulatory arrest → Transplant → Reperfusion X 15 minutes low Hct, low pressure, low flow blood → Rewarming 45 minutes → Weaning from bypass → Functional studies

Fig 1. Experimental protocol. (Hct = *hematocrit;* PGE1 = *prostaglandin* E_1.)

added 200,000 units of streptokinase and 10 mL of 50% dextrose. The heart was then harvested, inspected for any gross ventricular cavity thrombi, and placed in iced saline solution for a mean of 1.5 hours.

After donor harvest, recipient lambs were similarly anesthetized and cannulated, and a median sternotomy was performed. The pericardium was incised and fashioned into a cradle. The animals were heparinized with 4 mg/kg of sodium heparin. The ascending aorta was cannulated through a pursestring for arterial inflow and the right atrial appendage cannulated for venous egress to the pump-oxygenator. The animals were placed on bypass using an asanguineous prime and cooled to a rectal temperature of 20°C.

During bypass, prostaglandin E_1 administration was started at $0.1\ \mu g \cdot kg^{-1} \cdot min^{-1}$ and continued until 30 minutes before weaning from bypass. Simultaneously, a 5-mg nifedipine capsule was opened and its contents were inserted sublingually.

After cooling, the ascending aorta was cross-clamped and profound hypothermic arrest instituted. Cardiac transplantation was performed in our usual fashion, using the "dead" donor heart after excising the recipient's heart [2]. The venous cannula was reinserted into the donor's right atrium, the left atrial appendage was vented, and the lamb was placed back on bypass and rewarmed. With the aortic cross-clamp still in place, an 18-gauge cannula was inserted into the ascending aorta and connected to a separate line from the pump oxygenator, which delivered low hematocrit (0.08 to 0.12), low Ca^{2+} (ionized calcium, 0.3 to 0.5 ng/dL), warm blood at low pressure (30 mm Hg) and low flow (25 mL/min) for 15 minutes. The cross-clamp was then released, the hematocrit concentrated, and calcium repleted during a further 45-minute rewarming period. Bradycardia or temporary heart block was treated with boluses of 10 μg of isoproterenol, but none was given after cessation of bypass. All four hearts returned to sinus rhythm before weaning from bypass.

Results

After a total reperfusion period of 1 hour, all four hearts were weaned from bypass. Pressures were measured with indwelling needles at 1, 5, 15, and 30 minutes after bypass. At 30 minutes after bypass systolic aortic pressure was 80 ± 10 mm Hg, pulmonary artery pressure was 20 ± 5 mm Hg, and right and left atrial mean pressures were 9 ± 5 and 9 ± 2 mm Hg, respectively. Hemodynamics remained stable throughout the observation period, and no animal's condition deteriorated before termination of the experiment. All animals were then euthanized and their hearts recovered.

Comment

In recent years, efforts by Buckberg and his colleagues have suggested that cardiac ischemia of prolonged duration does not, in and of itself, lead to cardiac necrosis. In the past, irreversible cardiac muscle damage has been judged to occur after ischemia based upon pathologic studies of myocytes examined after myocardial blood flow restoration, presupposing that restoration of blood flow did not impart a reperfusion injury of its own [3]. Thus, periods of more than 15 minutes of warm ischemia have been thought to produce degrees of irreversible myocardial damage or necrosis, characterized pathologically by contraction bands and calcium deposition within swollen, deranged mitochondria [4]. Although little doubt exists that these changes do indeed occur with the restoration of normal arterial blood flow, it is now equally apparent that the restoration of such "normal" blood flow may be wholly or partially responsible for this "ischemic" necrotic damage via numerous mechanisms of reperfusion injury.

Altering the extent of reperfusion injury in the globally ischemic heart has been the subject of intensive laboratory and clinical work by ourselves and others in recent years. Our laboratory effort parallels our clinical findings that donor hearts obtained from infants resuscitated from sudden infant death syndrome, often after prolonged "down" times of 20 to 40 minutes, function well both in the short and medium term after being transplanted [5]. These clinical findings mirror our initial experimental results, that neonatal lamb hearts subjected to hypoxic arrest can be successfully transplanted and reanimated after 10 to 21 minutes of warm asystole [1]. The donors in these previous experiments were pretreated with prostaglandin and nifedipine, so that the present experiment adds additional potential risks of ischemic injury and reperfusion injury in an unpretreated donor.

The methods chosen for reperfusion in this model are based on easily controlled variables, which can be altered in a traditional bypass circuit. Specifically, (1) the use of a low-calcium cardioplegic agent such as Roe's solution may lessen the amount of extracellular calcium available for calcium paradox [6] and (2) similarly, the use of an asanguineous prime, with its resultant hemodilution, dramatically reduces ionized calcium levels in the reperfusate. Low calcium reperfusion alone significantly reduces reperfusion injury but (3) coupling this with a calcium channel blocker such as diltiazem further prevents calcium paradox within the myocardium [7]. (4) Addition of high amounts of dextrose to the cardioplegia solution or donor's circulation, or both, has been a mainstay of our clinical transplant program [2] and has been shown by Okamoto and his co-workers [8] to significantly improve myocardial function when included in cardioplegia solutions. (5) Controlled reperfusion with low-pressure, low-flow blood has been shown to significantly salvage myocardial contractility after prolonged ischemia, particularly if continued for more than 10 minutes [9, 10], and can be easily administered via any roller pump during initial rewarming. The mechanisms for this beneficial effect are unclear, but low-flow/low-pressure reperfusion most likely prevents myocardial edema and the washout out of "rounded" endothelial cells within the vasculature, allowing smooth muscle relaxing factor to continue to be produced, limiting the "no-reflow" phenomenon.

It is possible that other combinations of agents and maneuvers may produce better or at least equal effects on the recovery of severely ischemic myocardium. Indeed, the recovery of hearts after 30 minutes of warm ischemia while on cardiopulmonary bypass is possible, but represents an entirely different set of circumstances than described here. It was not surprising to us then, that in preliminary, unpublished experiments, we could not resuscitate adult goat hearts when nifedipine and prostaglandin were not given during reperfusion. In fact, the use of prostaglandin in this study stems directly from our unpublished clinical observation of improved myocardial performance and overall clinical condition in infants who received prostaglandin E_1 during and after transplantation. Its role as a vasodilator in preventing the no-reflow phenomenon is certainly additive to that of the other agents described above.

Finally, it must be noted that these results are preliminary and use temporary survival as the only end point of success. Numerous other studies are required to delineate whether this phenomenon occurs in other animals and in what ages. But ultimately, one must answer the question as to how long is "too long" before cell death will occur regardless of the methods of reperfusion. Our findings suggest that traditional concepts of cell death require extensive reexamination; such reexamination may eventually lead to the conclusion that cadaveric hearts can be used successfully in transplantation.

In conclusion, we have demonstrated in an experimental lamb model that hearts that have been "dead" for one half hour after death from exsanguination are capable of reanimation and can be used successfully for donor organs. Although these findings are preliminary, further refinements could result in the utilization of an entirely new source of organ donors, which are readily available and extremely common.

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DISCUSSION

DR JOHN C. BALDWIN (New Haven, CT): Not surprisingly from such an innovative group as the Loma Linda group, this is a provocative and interesting report which addresses, as they point out, a very important problem. As we all know, there are approximately 50,000 people who die every year of congestive heart failure and who might be considered as transplant candidates. Although xenografting may be the ultimate answer to biologic replacement, this certainly might be an important other line of pursuit. This, as Dr Gundry pointed out, is not an entirely new idea. There has been interest in this phenomenon, particularly in Japan where there has been difficulty with the concept of brain death and where there have been some reports of attempts of cadaveric resuscitation of potential heart grafts, particularly after Dr Wada's singular experience with an attempted heart transplantation in Japan.

I think Dr Gundry and associates have quite properly focused on the reperfusion injury as the most important aspect of this model, as one is not particularly surprised by the absence of structural damage, per se. I think that the study would have been enhanced, however, by inclusion of some biochemical data as well as some assessment of myocardial edema, which certainly has been seen in longer preservation standard heart transplantation.

I think that those of us who worked in Palo Alto with Dr Shumway when no one else was doing heart transplantations in significant numbers may be responsible for excessive conservatism in evaluating donors, and these criteria, of course, have crept into textbooks and federal documents and so on. One of the questions I would like to ask Dr Gundry is whether or not their experience with this model has in any way influenced their attitude toward hemodynamic instability or toward the issue of brief periods of cardiac arrest, which have been, of course, accepted but really limited to brief defibrillations.

Second, I believe that it is important to ask why the saline resuscitation was administered. This may have had a significant flushing effect. It is unclear, of course, as to whether or not there were any clots dissolved by the streptokinase that was given, but the saline administration may be an important aspect of this model and one that would not always be duplicated in dealing with trauma victims.

Finally, I would ask whether he can provide us with a rationale for the use of the prostaglandin E_1 pretreatment in the recipient and also apparently during the reperfusion of the heart.

DR GUNDRY: I would like to thank Dr Baldwin for those very excellent comments. First of all, this study did not evaluate any biochemical changes within the heart or the presence or absence of myocardial edema. This study is a preliminary study, and (at least in our laboratory) our feelings have always been to try and keep it simple. Survivability without inotropes, even for a short period of time, was our end point and certainly justifies continuing this study as to the exact biochemical changes that are occurring in these hearts.

In regard to whether this particular study and other studies that we are doing in our laboratory have changed what we do with our donor hearts, that is absolutely true. Actually both have been synergistic in a way. We have found in our infant transplantation experience that infants who die of sudden infant death syndrome, who account for a great number of our donors, have had anywhere from 10 minutes to 40 minutes of documented downtime, during which no resuscitation attempts were undertaken, and may have had up to 2 hours of cardiopulmonary resuscitation by experienced people before their hearts resumed functioning. Now, unfortunately all of these children eventually succumb to brain death, but the amazing thing that we found was that their hearts have been perfectly good! These hearts have been restudied on long-term follow-up for more than 5 years now, and we have found no detrimental changes in their long-term myocardial function. Indeed, as a result of these studies we have been prepared to take donors who are in fact moribund. Many of our donors, thankfully, have been refused by four or five other teams. We will frequently take donors on very high-dose inotropes with very little blood pressure, and the results have been very satisfactory.

Finally, in regard to the saline resuscitation, we made every attempt in this model to mimic a clinical model. The problem with intravascular thrombosis is a very real one in the lamb model. You heard yesterday in a canine model that up to 2 hours without heparin in a dead dog does not result in significant intravascular thrombosis within the lung. We did not find that to be true in the lamb. In fact, the lamb does have extensive intravascular thrombosis. The saline resuscitation, however, was attempted to mimic our observations that most of the patients in the emergency room resuscitation setting have had a saline resuscitation attempt or some other form of crystalloid infusion. In fact, most of these patients do have inherent anticoagulation from their resuscitation attempts, which is clearly evident in the operating room. So whether this does affect the application of this technique to a patient who arrives without a saline resuscitation will have to be shown by further results.

Videothoracoscopy: Improved Technique and Expanded Indications

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Current videoendoscopic technology and percutaneous techniques of exposure and dissection have been successfully applied to abdominal surgery with favorable results. Application of this technology to our practice of thoracoscopy is the basis of this report. Videothoracoscopy has been performed in 39 patients for the following indications: chronic pleural effusion, interstitial lung disease, mediastinal lymphadenopathy in lung cancer, persistent air leak after decortication, mediastinal mass, recurrent spontaneous pneumothorax, hydropneumothorax with persistent air leak, and pleural-based mass. The technique we employ includes lateral decubitus positioning and double-lumen endotracheal intubation with ipsilateral lung collapse. The videoscope, retractors, and instruments are introduced through separate 10-mm incisions. Percutaneous manipulation of instruments and the videoscope is guided by images produced on television screens without dissection, and if resection is performed, the incision is enlarged to allow specimen retrieval. Procedures performed using this technique include pleural biopsy, partial pleurectomy, lysis of adhesions, lung biopsies, staging lymph node biopsy, lung nodule biopsy, pleural-based mass resection, and mediastinal mass biopsy and resection. This videoendoscopic technique greatly improves visualization of thoracic anatomy, facilitating thoracoscopy and enhancing exploration of the chest. It is preferred over conventional thoracoscopy and, in some patients, reduces the magnitude of operation by avoiding thoracotomy.

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The incorporation of current video technology into conventional endoscopic methods has been perhaps the major advance in endoscopic diagnosis and therapy occurring in the past decade. Superior endoscopic image with a broader field and improved resolution have expanded the role of conventional endoscopy in a variety of medical and surgical fields. The utilization of this technology in our practice of thoracoscopy forms the basis of this report.

Material and Methods

Patients

From August 1, 1990, to October 23, 1991, 39 patients underwent videothoracoscopy at St. Thomas Hospital. This group included 25 men and 14 women of ages ranging from 21 to 77 years. The indications for thoracoscopic evaluation are listed in Table 1. In patients with chronic pleural effusion, thoracoscopy was performed after routine studies including thoracentesis and closed pleural biopsies were nondiagnostic. In patients with pleural-based masses, thoracoscopy followed percutaneous fine-needle aspirates that were inconclusive.

Techniques

In addition to the primary surgeon, the appropriate surgical team for videothoracoscopy includes a scrub nurse, a first assistant, and a video scope operator. The first assistant's role is primarily that of lung retraction, providing exposure for adequate visualization and percutaneous dissection performed by the surgeon. We have found, in general, that the most effective operating room positioning is for the surgeon to be on the patient side opposite the targeted pathology with the scrub nurse standing beside the surgeon. On the other side are the first assistant and camera operator. It is often necessary for the surgeon to change from one side to the other to gain the optimal approach to the target pathology.

We use a 16-power magnification laparoscope with either a 0-degree lens or a 30-degree lens, the latter of which is especially useful in visualizing the apex of the lung. A xenon light source provides illumination so that the image captured by the low-light-capability video camera is transferred to two high-resolution television monitors allowing both the surgeon and first assistant, while facing each other, to have simultaneous unobstructed views of the intrathoracic exposure. Eight-, 10-,

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Table 1. Indications for and Pathology Present at Thoracoscopy

Indication	Procedure	Pathology	No. of Patients
Chronic pleural effusion	Pleural biopsy	Nonspecific pleuritis	13
		Metastatic adenocarcinoma	2
		Metastatic squamous cell carcinoma	1
		Noncaseating granuloma	1
Pleural-based mass	Resection or biopsy of pleural-based mass	Metastatic adenocarcinoma	2
		Pleural fibrosis	2
		Hyalinized pleural plaque	2
		Melanoma	1
Staging for lung cancer	Lymph node biopsy	No evidence of metastasis	5
		Metastatic disease in aorticopulmonary window lymph node	1
Anterior mediastinal mass	Biopsy of anterior mediastinal mass	Hodgkin's disease	1
Posterior mediastinal mass	Resection of posterior mediastinal mass	Benign schwannoma	1
Spontaneous pneumothorax	Lung apex stapling and partial pleurectomy	Apical air leak	2
Interstitial lung disease	Lung biopsy	Lymphoid infiltrate	1
		Talc granulomas	1
Elevated hemidiaphragm	Thoracoscopic exploration	No pathology present	1
Hydropneumothorax with persistent air leak	Lysis of adhesions and partial pleurectomy	Incomplete lung expansion with adhesions	1
Persistent air leak after bleb stapling and decortication	Thoracoscopic exploration, thoracotomy	Multiple air leaks	1

and 12-mm trocars with sleeves that accommodate the video scope and retracting and dissecting instruments are available. The trocar sleeves have a portal for carbon dioxide insufflation, if needed. Retracting instruments consist of atraumatic grasping forceps which, though not designed for the lung originally, can retract the lung without undue trauma if used with caution. The grasping forceps are also employed in dissection as they and the scissors have an electrocautery adapter. Clip appliers and Endoloop applicators are available for hemostasis and tissue ligation. A new generation of percutaneous surgical staplers is being produced that allows linear stapling of the lung for biopsy and resection. The currently available models are 30 mm in length, but longer staplers with greater applicability should be forthcoming.

General endotracheal anesthesia is achieved through a double-lumen endotracheal tube. The patient is turned in the lateral decubitus position and secured with a "bean bag" blanket and tape, which allow for patient rotation from side to side. Sterile skin preparation and draping for a standard posterolateral thoracotomy is done.

After ipsilateral lung collapse, the initial trocar is inserted into the chest blindly and the video scope advanced through it. The trocars for the retraction and dissecting instruments are then inserted under videoscopic visualization, which can be important in preventing lung injury in patients with partial pleural symphysis. Adhesions between the lung and chest wall are electrocoagulated and then divided with scissors. The lung is retracted, allowing for examination of the chest. After adequate exposure is obtained, the procedure is completed and a chest tube is inserted.

Choice of the initial trocar insertion level depends on the surgical target. In general, approaching the target from inferiorly is best, and, of course, necessary if the target is apically located. The camera is inserted into the posterior axillary line, the retracting instruments on the target side of that line, and the dissecting instruments on the side opposite the target. Additional incisions are made as warranted.

Results

The pathologic results of the thoracoscopy are listed in Table 1. In the 17 patients undergoing thoracoscopy for chronic pleural effusion, 13 cases of nonspecific pleuritis were diagnosed. In 3 patients, 2 of whom had a history of lung cancer, metastatic cancer was found. In 1 patient, noncaseating granulomas were found on the pleural surface.

Of the 7 patients who underwent thoracoscopy to evaluate pleural-based masses, malignant disease was diagnosed in 3 patients, metastatic adenocarcinoma in 2, and melanoma in 1 patient. The remaining 3 patients had benign pleural processes.

Thoracoscopy was used to stage lung cancer in 6 patients who had enlarged aorticopulmonary window lymph nodes by computed tomography. Biopsy in one of these patients revealed metastatic lung cancer, whereas in the other 6, no metastases were identified, a finding that was later confirmed at thoracotomy.

Hodgkin's disease was diagnosed by biopsy of an anterior mediastinal mass, and a benign schwannoma was resected from the paraspinal posterior mediastinal space. Two patients with recurrent spontaneous pneumothorax underwent bleb stapling and apical pleurectomy. One patient with a history of mediastinal lymphoma underwent thoracoscopy to investigate an acutely elevated hemidiaphragm. No pathology was discovered. Hydropneumothorax with persistent air leak after pneumothorax associated with prolonged mechanical ventilation was present in 1 patient. At thoracoscopy, adhesions were lysed between the lung and chest wall, which allowed full lung expansion. We attempted thoracoscopy on 1 patient with incomplete lung expansion and persistent air leak after decortication and bleb stapling. Lung injury occurred when the initial trocar was inserted, resulting in hemorrhage from the lung requiring thoracotomy for hemostasis. Two patients with interstitial lung disease underwent lung biopsy. Talc granulomas and lymphoid infiltrate were the findings.

Comment

The value of thoracoscopy in evaluation of pleural disease is well documented, and thoracoscopy is used routinely in our hospital. Conventional thoracoscopy can be limited by limited field of vision with suboptimal resolution, inadequate exposure, and the inability to perform simultaneous dissection while visualizing the lung or pleural surface. We believe that the videothoracoscopy method we describe offers several real advantages over conventional thoracoscopy.

Improved visualization of the intrathoracic anatomy is one of the primary advantages of this method. It results from an expanded visual field (thus surgical field) with superior illumination. Image magnification results in improved resolution that allows tedious percutaneous dissection. Moreover, this dissection can be performed simultaneously by the surgeon as, having assistants to operate the video scope and provide retraction, he or she is free to use the retracting and dissecting instruments as needed.

Another important advantage of our method is the potential to avoid thoracotomy in some patients. Lung biopsy, resection of pleural-based masses, bleb stapling, and pleurectomy can all be accomplished safely with this technique. We expect that with improved instruments such as larger staplers and better retracting instruments, the indication for thoracoscopic procedures will expand further.

Biopsy of aorticopulmonary window lymph nodes can be performed as a staging procedure by using this technique. Although technically a bit more difficult than a Chamberlain procedure, it is better tolerated by patients and can accomplish the same goal, yet avoid anterior mediastinotomy. Should we be unable to perform a biopsy on the lymph nodes as planned (the patient is made aware preoperatively of this possibility), we proceed with the more invasive alternative.

The most difficult aspect of this technique is exposure. For optimal exposure, lung collapse is mandatory and, therefore, the double-lumen endotracheal tube is a necessity. We have not found it necessary to use carbon dioxide insufflation to accomplish lung collapse. Retraction of the collapsed lung often becomes the key to exposure. The presently available instruments were designed for intraabdominal retractions and can harm the lung if not used cautiously. We have found that retraction of the lung is more safely accomplished and provides better exposure by securing the lung in the atraumatic forceps and pushing it away from the target area rather than pulling it away. Also, with the patient secured in the lateral decubitus position, rotation of the table can allow the lung to fall to the appropriate side. Maintaining optimum exposure for prolonged dissection requires meticulous hemostasis that is achieved by the liberal use of the electrocautery adaptors for the dissecting instruments.

The difficulty produced by a bloody field cannot be understated as the advantage of improved visualization is immediately negated. Constant attention to hemostasis by liberal use of electrocautery and vessel clips can help to avoid this problem.

A challenging aspect of this technique is encountered in the patient with pleural adhesions. Pleural visualization and evaluation in the patient with pleural symphysis is impossible by any method other than thoracotomy, and unless the pleural space is relatively free, that is, unless we believe we can enter the pleural space initially and gain access to adhesions to lyse them and thereby increase our visualization, we do not attempt thoracoscopy by any method. The risk of lung injury with pneumothorax and air embolus is substantial on the initial trocar insertion, and although subsequent insertions may be monitored videoscopically, precautions should be taken before the initial insertion if one suspects difficulty. In that case, we make our initial incision large enough to admit a finger into the chest to verify some sort of space between the lung and chest wall or to allow room to overlap the lung away from the chest wall to produce such a space. The trocar can then be safely inserted.

Although this technique varies profoundly from standard thoracic surgical procedures, it has exciting potential for avoiding thoracotomy in selected patients. The magnitude of the operation is then reduced, with obvious benefits for the patient.

DISCUSSION

DR JAMES W. MACKENZIE (New Brunswick, NJ): I would like to thank Dr Coltharp and his colleagues for presenting this subject. Under the direction of Dr Ralph Lewis, Chief of our Section of General Thoracic Surgery, we have had intense interest in what we have termed videoscopic thoracic surgery for the last year and a half. We have done some 100 cases, including 25 or so definitive resections of tumors, either primary or secondary. In addition, we have also applied this technique to neurogenic tumors as you have shown, to bronchogenic cysts, to the creation of pericardial windows, and indeed have carried out two lobectomies with this technique. Dr Lewis has put on courses for about 60 people from various centers throughout the United States who are identified with general thoracic surgery, and they have all gone back and adopted this procedure with enthusiasm.

Nevertheless, there are some questions I have to raise. As we look at it, we are not sure that we necessarily make the operation any shorter. Indeed, some of these cases take longer. I would be interested in your experience in this regard. Second, although we have in general been able to have the patients leave the hospital within 3 or 4 days, there is the occasional patient who stays longer, and so I would like to know if you have any indication about the length of hospitalization that your patients had as compared with the usual approach.

Finally, I think it is obvious that this is a promising new technique for the general thoracic surgeon. Where it will fit in will depend on ingenuity and new instrumentation, but I think it is important for all of us to not write it off as just another gadget as was done by some general surgeons not too long ago for cholecystectomy.

DR COLTHARP: As we are still on the learning curve for this procedure, the length of operation initially was frustrating. This is not a technique with which we are familiar, that is, percutaneous manipulations of instruments to dissect in the chest. I do think, though, that patients who avoid thoracotomy, such as patients with recurrent spontaneous pneumothorax, neurogenic tumor excision, and lung biopsy, are able to leave the hospital sooner. I do not have those data with me.

I would like to just make a comment on new technology and instruments. This, I am sure you are aware, is a new field for the medical instrument manufacturers also, and I know that some of the new instruments that are helpful especially in retracting the lung are disposable. I do have some hesitation in committing myself to using disposable instruments in all of these cases.

DR F. HAMMOND COLE, JR (Memphis, TN): I just wanted to commend you on this very nice series. I would agree with the other discussant that it is vital for us to be involved in this technology early on or it is going to go to someone else, much as did diagnostic endoscopy. Our experience has pretty much paralleled yours, except that we have seen a higher percentage of malignant effusions overall. What do you do with malignant effusion through the thoracoscope? Have you found any literature on or technique for sclerosing these patients?

DR COLTHARP: Well, it is not extremely difficult to perform a pleurectomy, provided there is not previous pleural synthesis and not a lot of adhesions that restrict your manipulation of the instruments, and that is what we have used.

Colorectal Lung Metastases: Results of Surgical Excision

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Between 1960 and 1988, 139 consecutive patients underwent pulmonary resection for metastatic colorectal carcinoma. Median interval between colon resection and lung resection was 34 months. Ninety-eight patients (70.5%) had a solitary metastasis. Wedge excision was performed in 68 patients, lobectomy in 53, lobectomy plus wedge excision in 9, bilobectomy in 4, and pneumonectomy in 5. Operative mortality was 1.4%. Localized extrapulmonary colorectal cancer was also resected in 20 patients. Median follow-up was 7 years (range 1 to 20.4 years). Overall 5- and 20-year survival was 30.5% and 16.2%, respectively. Five-year survival for patients with solitary metastasis was 36.9%, as compared with 19.3% for those with two metastases ($p < 0.05$) and 7.7% for those with more than two ($p < 0.01$). Patients with normal carcinoembryonic antigen had a 5-year survival of 46.8% versus 16.0% for patients with increased levels ($p < 0.01$). Five-year survival for patients with resected extrapulmonary disease was 30.0% versus 30.7% for those without extrapulmonary cancer (p = not significant). Repeat thoracotomy for recurrent metastases was done in 19 patients. Five-year survival after the second lung resection was 30.2%. We conclude that resection of colorectal lung metastases is safe and effective, that resectable extrapulmonary disease does not necessarily contraindicate pulmonary resection, and that repeat thoracotomy is warranted in selected patients with recurrent colorectal lung metastases.

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Blalock [1] first reported pulmonary resection for metastatic colorectal carcinoma in 1944. Since then, more than 500 patients have been reported to have undergone pulmonary resection for this disease [2–17]. Yet pulmonary resection remains controversial, and the factors that determine long-term prognosis are not completely understood. Because most series are limited by small numbers of patients, the role of repeat thoracotomy for recurrent cancer has also not been well defined. Similarly, few reports have addressed the role of pulmonary resection in the presence of localized extrapulmonary disease. The purpose of this review was to analyze our entire experience with pulmonary resection for metastatic colorectal cancer in an attempt to answer these questions.

Material and Methods

Between January 1, 1960, and December 31, 1987, 139 patients underwent curative pulmonary resection for metastatic colorectal carcinoma at our institution. Resection was considered curative if all known pulmonary cancer was removed at thoracotomy. Patients who had complete resection of all known extrapulmonary disease were also included. Excluded were patients who had pulmonary biopsy only or incomplete resection. The record of each patient was reviewed for age and sex; location, grade, and stage of primary colorectal cancer; tumor-free interval; prethoracotomy carcinoembryonic antigen (CEA) level; location, number, diameter, and grade of pulmonary metastases; extent of pulmonary resection; complications; and long-term survival.

All resected colorectal tissue was reviewed to determine Broders' tumor grade [18] and Dukes' stage (Astler-Coller modification) [19]. Pulmonary metastases were also graded by Broders' classification [18]. When multiple metastases were present, the highest grade and largest diameter were recorded. To avoid misinterpretation of a primary lung adenocarcinoma with a colorectal metastasis, those pulmonary neoplasms in question were compared histologically with the original colorectal tissue, stained for mucin, and examined by a second pathologist.

Operative mortality included patients who died within the first 30 days after thoracotomy and those who died later but during the same hospitalization. Survival was estimated by the method of Kaplan and Meier [20] using the date of the pulmonary resection as the starting point. The influence of variables on survival was analyzed using the log-rank test for discrete variables [21] and the proportional hazards model of Cox for continuous variables [22].

Clinical Findings

There were 73 men and 66 women. Median age was 64 years (range, 32 to 84 years). Forty-four patients (31.7%) were 70 years of age or older. The primary colorectal neoplasm was a solitary adenocarcinoma in all patients and was located on the right (15 cecum, 11 ascending, and 3 transverse colon) in 29 patients (21.0%) and on the left

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(10 descending colon, 40 sigmoid, and 59 rectum) in 109 (78.4%). In 1 patient the location could not be determined.

Fifty-six patients had their colorectal operation at another institution. An anterior resection was performed in 38 patients, a segmental resection in 36, an abdominoperineal resection in 29, a hemicolectomy in 25, a local excision in 3, a Hartmann procedure in 2, and total abdominal colectomy in 1. The extent of resection could not be determined in 5 patients. The neoplasm was classified as Dukes' A in 1 patient, Dukes' B in 74, Dukes' C in 52, and unknown in 12. Two patients received postoperative chemotherapy, 7 had radiation therapy, and 1 had both.

Pulmonary metastases were asymptomatic in 119 patients (85.6%). Signs and symptoms in the remaining 20 patients included cough in 8, pneumonia in 5, hemoptysis in 4, pain in 4, and dyspnea in 2. Conventional chest roentgenograms revealed a solitary pulmonary nodule in 119 patients (85.6%), multiple unilateral nodules in 15 (10.8%), bilateral nodules in 3 (2.2%), and lobar atelectasis in 2 (1.4%). Computed tomography (CT) was available during the last half of the time period in this study and was performed in 64 patients, 16 of whom were found to have additional pulmonary nodules. After all roentgenographic examinations, 6 patients were demonstrated to have bilateral pulmonary lesions.

All patients were evaluated for local recurrence of their colorectal cancer. Barium enema, endoscopy, and abdominal CT were the procedures most commonly employed. Bone and brain scans were performed if there were clinical signs suggestive of metastases in these areas. The level of CEA was measured in 52 patients and was elevated (≥5 ng/mL) in 24.

All pulmonary resections were performed at our institution. Pulmonary resection followed colon resection in 136 patients; 3 patients, however, had initial lung resection which led to the subsequent diagnosis of a colorectal cancer. The median interval between colorectal resection and lung resection in the 136 patients was 34 months (range, 1 week to 13 years). Fifty-one patients had a tumor-free interval of less than 2 years. Lateral thoracotomy was performed in 133 patients and median sternotomy in 6. No patient underwent staged or simultaneous bilateral thoracotomies. Wedge excision was done in 68 patients and consisted of a single wedge in 50, two in 15, three in 2, and four in 1. Fifty-three patients had lobectomy, 4 had bilobectomy, 5 had pneumonectomy, and 9 had lobectomy combined with wedge excision. At operation, pulmonary metastases were unilateral in 134 patients (68 right and 66 left) and bilateral in 5; 1 of the 6 patients with preoperative bilateral pulmonary lesions was found to have granulomatous disease on one side. Ninety-eight patients had solitary metastases, 28 had two metastases, 10 had three, and 1 each had four, five, and six. One patient had a solitary grade 2 adenocarcinoma consistent with colorectal metastasis and a synchronous primary grade 3 squamous cell lung cancer (T2 N0 M0). Twelve patients (8.6%) were found to have lymph node involvement; 8 had peribronchial metastases, 2 had hilar metastases, and 2 had peribronchial lymph node invasion by direct extension. Median diameter of the colorectal metastases was 2.5 cm (range, 0.5 to 10.0 cm). Histologically, the metastases in 4 patients were classified as Broders' grade 1, 126 as grade 2, 8 as grade 3, and 1 as grade 4.

Twenty patients also underwent resection of localized extrapulmonary colorectal cancer. Fifteen patients had solitary metastases which were located in the liver in 7 patients, brain in 5, pelvis in 2, and abdominal wall in 1. Five patients had recurrent cancer at bowel anastomoses. Resection was complete in all 20 patients, 3 of whom had concomitant lung and extrapulmonary resection.

Table 1. Postoperative Complications

Complication	No. of Patients	
Respiratory	10	
Retained secretions		3
Atelectasis		3
Bronchopleural fistula		2
Pleural effusion		1
Pulmonary embolism		1
Arrhythmia	2	
Hemorrhage	1	
Ileus	1	
Urinary retention	1	
Venous thrombosis	1	

Results

Complications (Table 1) occurred in 17 patients (12.2%). The majority were pulmonary. Two patients died (operative mortality, 1.4%). One death was caused by pulmonary artery hemorrhage the night of operation in a patient who had undergone lobectomy for a solitary metastasis. The other death occurred on day 16 owing to adult respiratory distress syndrome in a patient who had undergone pneumonectomy for synchronous primary squamous cell lung cancer and colorectal metastasis. No deaths occurred in the 68 patients who had wedge excision, 1 in the 66 patients undergoing lobectomy (1.5%), and 1 in the 5 patients undergoing pneumonectomy (20.0%). No deaths occurred in patients 70 years of age or older.

Follow-up was complete in 136 of the 137 operative survivors (99.3%). Median follow-up was 7 years (range, 1 to 20.4 years). The 1 patient who was lost, however, was followed up for 8 years without evidence of recurrent colorectal cancer. Metastatic colorectal cancer recurred in 101 patients (74.3%) (Table 2). Recurrence was limited to the lungs in 38 patients, the abdomen in 16, the brain in 7, and bone in 3. Recurrence was to multiple organ systems in 37 patients and involved the lungs in all. Altogether, recurrence after pulmonary resection involved the lung in 75 patients (74.3%). Thirty-one patients currently are alive, 30 free of disease. Cause of death in the remaining 105 patients was recurrent colorectal cancer in 95, cardiac

Table 2. Site of First Recurrence After Thoracotomy

Site	No. of Patients	
Solitary	64	
Lung		38
Abdomen		16
Brain		7
Bone		3
Multiple	37	
Lung + abdomen		16
Lung + brain		8
Lung + bone		4
Disseminated		9
Total	101	

disease in 5, and stroke in 3. The remaining 2 patients died of primary squamous cell lung cancer that developed 2 years after pulmonary resection for metastatic colorectal cancer.

Estimated 5-, 10-, and 20-year survival for all patients was 30.5%, 19.1%, and 16.2%, respectively (Fig 1). Survival was not influenced by age or sex; location, grade, or Dukes' stage of the colorectal cancer; pulmonary signs and symptoms; location, grade, or diameter of the pulmonary metastases; or extent of pulmonary resection. Likewise, 5-year survival for the 51 patients with a tumor-free interval of less than 2 years was 27.9% and did not differ significantly from the 31.8% observed for the 85 patients with a tumor-free interval of greater than 2 years. Similarly, the 30.0% 5-year survival observed for the 20 patients with resected extrapulmonary disease did not differ significantly from the 30.7% survival observed in the 119 patients without extrapulmonary disease (Fig 2). Only the number of pulmonary metastases and serum CEA level influenced survival. Five-year survival was 36.9% for patients with solitary metastases (Fig 3), as compared with 19.3% for patients with two metastases ($p < 0.05$) and 7.7% for those with more than two ($p < 0.01$). However, survival observed in patients with two metastases did not differ significantly from that of patients wit more than two. Five-year survival for the 28 patients wit a prethoracotomy CEA level of less than 5 ng/mL wa 46.8% (Fig 4), as compared with 16.0% for the 24 patient with a CEA level of 5 ng/mL or greater ($p < 0.01$). Mor importantly, all 24 patients who had an elevated prethc racotomy CEA level had development of recurrent colc rectal cancer after thoracotomy, and 23 (95.6%) have diec Thirty-one patients with a solitary nodule had CEA dete minations. The 21 patients with CEA levels of 5 ng/mL c less had a 5-year survival of 46.6% as compared with onl 10.0% survival for the 10 patients whose CEA level wa greater than 5 ng/mL ($p < 0.01$).

Survival for the three decades of this study is shown i Table 3. Although the 13.3% 5-year survival observe during 1960 to 1969 was less than the 34.5% and 31.7' survival in the subsequent two decades, respectively, th: observation was not significant ($p = 0.15$). Likewise, th 18.1% 5-year survival observed for patients with solitar

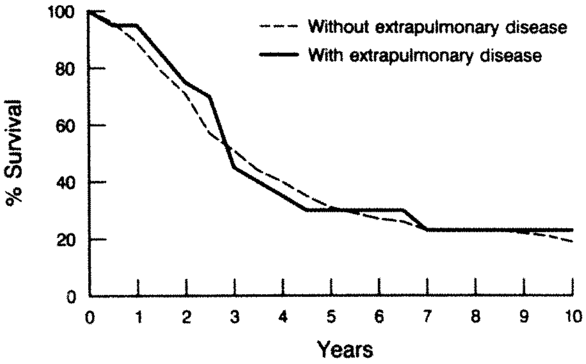

Fig 2. Probability of survival (death from any cause) of 119 patients undergoing curative pulmonary resection for colorectal carcinoma met astatic to the lungs without extrapulmonary disease, as compared wit 20 patients undergoing curative resection of both pulmonary and extrapulmonary disease (p = not significant). Zero time on abscissa represents the date of pulmonary resection.

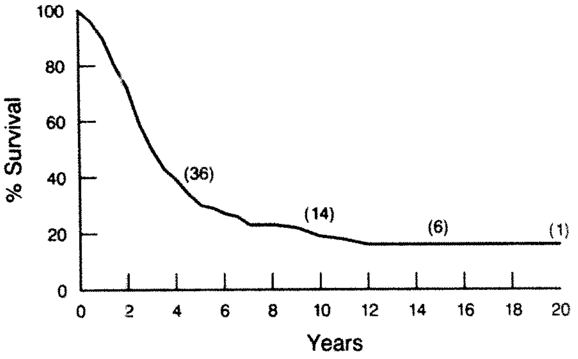

Fig 1. Overall probability of survival (death from any cause) of 139 patients undergoing curative pulmonary resection for colorectal carcinoma metastatic to the lungs. Zero time on abscissa represents the date of pulmonary resection. (Number in parentheses represents number of patients at risk.)

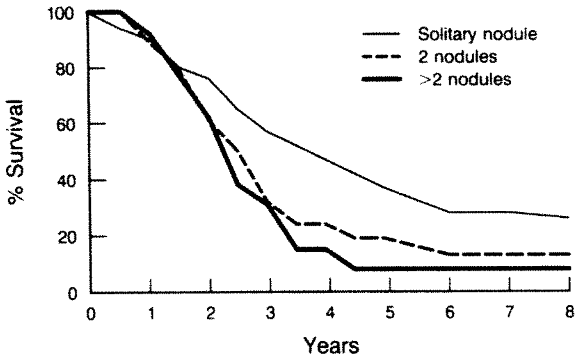

Fig 3. Probability of survival (death from any cause) of 98 patients undergoing curative pulmonary resection for a solitary colorectal carc noma metastatic to the lungs, as compared with 28 patients with twc pulmonary metastases (p < 0.05) and 13 patients with more than tu (p < 0.01). Zero time on abscissa represents the date of pulmonary resection.

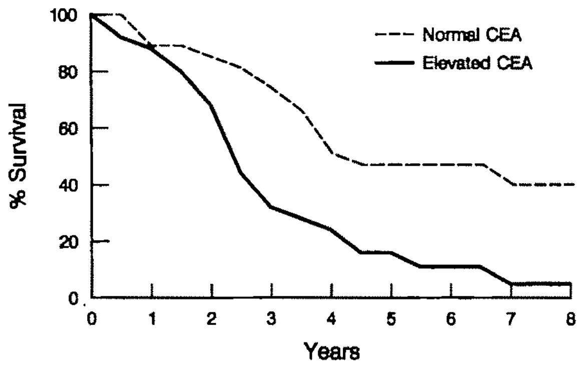

Fig 4. Probability of survival (death from any cause) of 29 patients undergoing curative pulmonary resection for colorectal carcinoma metastatic to the lung with a normal serum carcinoembryonic antigen (CEA) level, as compared with 24 patients with an elevated level (p < *0.01). Zero time on abscissa represents the date of pulmonary resection.*

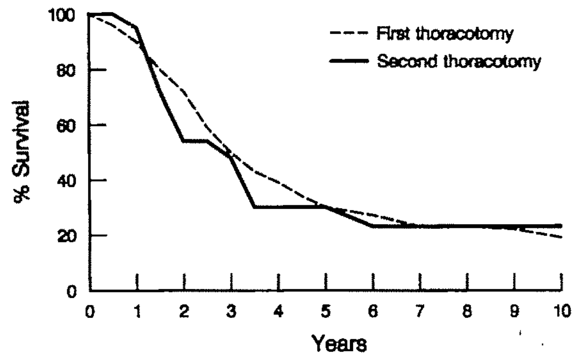

Fig 5. Probability of survival (death from any cause) of 120 patients undergoing a first thoracotomy for colorectal carcinoma metastatic to lungs, as compared with 19 patients who underwent a second repeat thoracotomy for recurrent colorectal carcinoma metastatic to the lungs. Zero time on abscissa represents the date of pulmonary resection for both the first and second thoracotomies.

pulmonary metastasis in the 1960s was not significantly less than the 43.2% observed during the 1970s and 36.3% during the 1980s ($p = 0.12$).

Nineteen patients underwent a second thoracotomy for recurrent colorectal cancer. A wedge excision was performed in 7 patients, lobectomy in 6, completion pneumonectomy in 3, and combined lobectomy and wedge excision in 3. The median interval between the first and second pulmonary resection was 17 months (range, 7 months to 5 years). At the time of second thoracotomy, 11 patients had a solitary metastasis, 5 had two metastases, 2 had three, and 1 had four. There were no major postoperative complications and no operative deaths. Five-year survival for all 19 patients from the date of the second thoracotomy was 30.2%, which was similar to the overall 5-year survival of 30.5% observed after the first thoracotomy (Fig 5). Four patients (21.1%) were living without recurrence more than 5 years after the second lung resection.

Four patients had a third pulmonary resection for recurrent cancer. One patient is alive 7 years after the third thoracotomy without evidence of cancer; 2 died of recurrent cancer 13 and 36 months after the third thoracotomy. The last patient had two additional thoracotomies but died of recurrent cancer 24 months after the fifth resection.

Table 3. Five-Year Survival by Decade

	Overall		Solitary		Multiple	
Decade	No.	Percent	No.	Percent	No.	Percent
1960–1969	15	13.3	11	18.1	4	0
1970–1979	55	34.5	44	43.2	11	0
1980–1987	69	31.7	43	36.3	26	24.7
Total	139	30.5	98	36.9	41	

Comment

Cancer of the colon and rectum is the second most common malignancy in the United States, occurring in approximately 5% of US-born men and 6% of women [23]. In 1991, colorectal adenocarcinoma will develop in approximately 157,500 patients in the United States [24]. Median survival for patients with disseminated disease is less than 10 months, and less than 5% will survive 5 years [25]. Many patients will have development of pulmonary metastases some time during the course of their illness, but in only a small percentage will the metastasis be solitary [26–28]. To date, no effective chemotherapeutic treatment is available for colorectal carcinoma metastatic to the lungs. Consequently, resection of pulmonary metastases has been accepted as appropriate therapy by many physicians.

McCormack and Attiyeh [2] have estimated that approximately 1,000 patients per year will have development of resectable pulmonary metastases from colorectal cancer, and most of these patients will have solitary nodules that must be differentiated from primary lung cancer [29, 30]. Roentgenographic evaluation, bronchoscopy, and transthoracic biopsy often cannot differentiate between the two. An extensive preoperative evaluation to differentiate the two neoplasms, however, is not necessary because surgical resection is the appropriate treatment for both if the lesion is solitary without evidence of regional or distant spread.

An orderly approach to searching for disseminated colorectal cancer is indicated. A thorough clinical examination should be performed, looking for signs and symptoms of metastases to other sites. Liver function tests and measurement of the serum CEA level should be performed; if the CEA level is elevated, a thorough search should be undertaken for metastatic disease. Bone scans and head CT should be reserved for patients with abnormal laboratory findings or symptomatic patients as only a small percentage of asymptomatic patients have unsuspected metastases. There should be no evidence of recurrent carcinoma at the primary colorectal location. A barium enema, colorectal endoscopy, or both should be performed on every patient. If the patient is otherwise in good health and evaluation reveals that the lung is the only known site of metastases, then CT of the chest and upper abdomen should be performed to exclude other pulmonary and liver metastases. In our series, CT demonstrated additional pulmonary nodules in 20% of patients.

Resection of pulmonary metastasis from colorectal cancer is associated with a 5-year survival of 13% to 61% [2–9, 12–14, 16, 17]. Our overall survival of 30.5% compares favorably. Patients with a normal CEA level and a solitary nodule had the best 5-year survival (46.6%). In contrast, an elevated CEA level was an ominous prognostic finding in that all of our patients with an elevated CEA level had development of recurrent colorectal cancer after thoracotomy, and 96% have died. However, we do not consider an elevated CEA level an absolute contraindication to pulmonary resection, as 5-year survival was still 16%. Likewise, patients with multiple nodules should not necessarily be denied resection, as 5-year survival after pulmonary resection in our most recent decade was approximately 25%. Similarly, a short tumor-free interval should not by itself preclude pulmonary resection. Although others have reported decreased survival in patients with short tumor-free intervals [5, 7, 14], we observed identical survival in patients with less than 2-year intervals when compared with those with greater than 2-year intervals.

Traditional criteria for resection of colorectal pulmonary metastases include absence of extrapulmonary disease. However, in our series the presence of resectable colorectal cancer in the liver, brain, bowel, and abdominal wall was not associated with a decreased survival; overall 5-year survival was identical to that of patients without extrapulmonary disease. Unquestionably, these patients with colorectal cancer in different organ systems were highly selected. However, others have reported similar good results [7, 8, 32]. Thus, we advocate combined or staged surgical resection in carefully selected patients with solitary lesions in different organ systems, although this situation will be relatively uncommon.

Limited wedge excision remains our procedure of choice for metastatic colorectal cancer. In our experience, mortality was zero after this procedure and long-term survival was similar to that of more extensive resections. We prefer median sternotomy for patients with bilateral lesions except in patients with previous sternotomy or if the lesions are located posterior to the hilus, especially on the left. These latter patients are better treated with bilateral staged thoracotomies. Lobectomy and pneumonectomy should be performed only if necessary to remove all disease or if the diagnosis of metastatic disease cannot be made with certainty at the time of operation. We believe that if the possibility exists that the lesion is a primary lung cancer, formal pulmonary resection is appropriate. In our patients, there were no deaths in patients 70 years of age or older; thus, age alone should not be a contraindication to resection.

Close surveillance is essential to detect recurrent disease at an early and potentially curable stage after pulmonary resection. We recommend biannual chest roentgenogram, chest CT, and serum CEA measurement in those patients who have had pulmonary resection for metastatic colorectal cancer. Follow-up must be life-long because recurrent pulmonary metastases developed as long as 5 years after the first pulmonary resection.

Several authors have advocated repeat thoracotomies for recurrent disease [13, 16, 28, 33, 34]. Our conclusion is similar. Survival in our patients who underwent a second thoracotomy was identical to survival observed in patients having only one. Importantly, patients undergoing repeat thoracotomy had no increase in either morbidity or mortality. Thus, we continue to offer at least one repeat thoracotomy to those selected patients who can tolerate further resection. Are three or more repeat thoracotomies indicated? Our patient numbers are too small to accurately determine. Nonetheless, 1 of 4 patients who had three repeat thoracotomies was alive and well 7 years after the third thoracotomy without evidence of cancer.

We conclude that resection of colorectal pulmonary metastases is safe and effective, and that selected patients with localized extrapulmonary disease are candidates for both extrapulmonary and pulmonary resections. Careful follow-up is warranted as patients with recurrent pulmonary metastases can undergo repeat thoracotomy with acceptable long-term survival.

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DISCUSSION

DR KAMAL A. MANSOUR (Atlanta, GA): I really enjoyed this report. The work reflects the excellence of the papers that come from the Mayo Clinic. What impressed me most is the large number of patients evaluated.

I have four points to discuss. First is the histology. The histology of most cases of metastatic colon cancer to the lung is so characteristic that you had 3 patients in whom the chest was opened first and the diagnosis of colon cancer was made, and we had the same experience. You can work up a solitary nodule in the lung and you resect it and then the pathologist will tell you, this is almost certainly colon cancer. This is unlike the cases that are going to be presented later on today and tomorrow on metastatic breast cancer and metastatic renal carcinoma, where the pathologist tells you it is compatible but not characteristic. Ideally, if the diagnosis of colon cancer is made first, then controlling the primary disease before addressing the pulmonary metastases is highly recommended.

The second point is a question. Did you find any relationship between the initial depth of invasion of the tumor (Dukes' stage) and the number of metastases to the lung? Do we get more metastases with more invasive tumors?

The third point is in reference to the 12 patients with nodal metastases you mentioned. In your experience, what is the significance of lymph node invasion when we go for resection of metastatic disease? Does it affect your survival rate?

Fourth, you have an excellent 30.5% 5-year survival for the first operation or for even the second operation. You stated that survival depends on two main factors, the number of the pulmonary metastases and the level of the CEA. How about bilateral disease? How about synchronous versus metachronous metastases? Do they affect survival or prognosis?

DR McAFEE: We agree that colon metastases have a distinctive histologic pattern in that they are low grade and produce mucin. Your second question dealt with depth of invasion of the primary colon cancer. We did not specifically analyze the effect of that on the number of pulmonary metastases, but we did find that the Astler/Coller modification of Dukes' classification had no effect on survival. More than one third of our patients had lymph node metastases at the time of colon resection, and they did as well as those who had negative lymph nodes. In contrast, we do not know the effect of mediastinal lymph node metastases on survival because lymph node sampling was not routinely done. Regarding your last question, only 3 of our patients had synchronous colon and pulmonary metastases, so we cannot make a statement about the significance of that either.

DR JOE B. PUTNAM, JR (Houston, TX): At the University of Texas M.D. Anderson Cancer Center we have resected colorectal metastases from 45 patients over a 7-year period. The 3-year survival for all patients was 51%. As in your series, most patients had a single thoracotomy and all had resectable disease. We found no additional predictors of postthoracotomy survival, but CEA level was not examined. I have three questions.

First, are there any better means than CEA measurement and visual histology to determine the origin of these metastases? Second, extrathoracic metastases have routinely been a contraindication to pulmonary resection; however, in your series 20 patients underwent resection of extrathoracic metastases in addition. How were these patients selected, and was pulmonary resection performed in the face of diffuse extrathoracic disease? Finally, how were the majority of patients with recurrence treated?

DR McAFEE: There is no foolproof way of determining the origin of a pulmonary adenocarcinoma. Clearly, an elevated CEA level adds to the certainty of a colon origin.

Those patients who had extrathoracic metastases resected were obviously very highly selected, and we included only those patients who had complete resection. Generally, these were patients with either a solitary extrapulmonary metastasis or an anastomotic bowel recurrence. We did not operate on any patient who had evidence of disseminated disease.

Your last question dealt with recurrent cancer, which our institution tends to treat surgically whenever possible. Unfortunately, the majority of recurrences are not resectable, and these patients are then treated by a variety of medical means, including chemotherapy and radiation therapy.

DR WILLIAM A. COOK (North Andover, MA): You had two criteria that raised the survival level to 30%: one was a solitary lesion, the other was a normal CEA level. Can you tell us what the survival was when both of those two criteria were met, that is, a normal CEA level and a solitary lesion?

DR McAFEE: Thirty-one of our patients with a solitary pulmonary nodule had CEA determinations. The 21 patients who had a normal CEA level had a 5-year survival of 46.6% as compared with only 10.0% survival for the 10 patients whose CEA level was elevated.

Notice From The Society of Thoracic Surgeons

New Abstract Deadline Date

The abstract due date is Monday, August 17, 1992, for all papers submitted for the Twenty-ninth Annual Meeting of The Society of Thoracic Surgeons, which will be held at the San Antonio Convention Center in San Antonio, Texas, January 25–27, 1993. No abstracts received after this date will be considered for presentation. The deadline for receipt of films and video tapes is Monday, August 3, 1992. Details are available in the Call for Abstracts published in this issue of *The Annals* or from Society headquarters, 401 N Michigan Avenue, Chicago, IL 60611 (telephone: (312) 644-6610).

Heparin-Induced Thrombocytopenia in Open Heart Surgical Patients: Sequelae of Late Recognition

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Most patients undergoing open heart operations have had exposure to heparin for diagnostic and/or therapeutic procedures. Heparin antibody formation and heparin-induced thrombocytopenia with repeat heparin administration can cause high morbidity and mortality from thrombotic complications, especially when delay in diagnosis occurs. From 1981 to 1991, heparin-induced thrombocytopenia was diagnosed in 82 of 4,261 open heart surgical patients (1.9%). Platelet counts less than 100 × 10^9/L (100,000/µL) or new or recurring thrombotic events prompted suspicion of heparin-induced thrombocytopenia. Heparin-dependent antibody was diagnosed preoperatively in 12 patients (group I) and postoperatively in 70 patients (group II). Heparin was not given postoperatively in group I patients, and complications in this group were limited to bleeding in 3 patients. There were no thromboembolic events and all patients survived. Group II patients had late recognition of heparin-dependent antibody postoperatively, and heparin exposure was continued for varying periods postoperatively. Thirty-seven group II patients (53%) had bleeding complications and 31 (44%) had thromboembolic complications. These complications led to death in 23 group II patients (33%). Heparin-dependent antibody may occur in patients having open heart operations and is a major cause of morbidity and mortality if not diagnosed early with cessation of heparin therapy.

(Ann Thorac Surg 1992;53:787–91)

Heparin-induced thrombocytopenia is caused by an immune mechanism in which antibodies and complement bind to platelets in the presence of heparin [1]. Although the transient form of heparin-induced thrombocytopenia was first recognized in animals in 1941 [2] and in humans in 1962 [3], the delayed form was first identified as a clinical entity in 1973 [4]. It occurs in approximately 4% to 5% of patients from 4 to 15 days after the initial exposure to heparin therapy (it may occur on the first day of exposure) and is often associated with life- or limb-threatening consequences [5].

Most patients undergoing open heart operations have had previous exposure to heparin and will require reexposure. Early testing for the presence of heparin-associated antiplatelet antibodies and, when the antibodies are present, cessation of all forms of heparin exposure can reduce the complications of heparin-induced thrombocytopenia [6]. The late recognition of heparin-induced thrombocytopenia in the postoperative period may be associated with an increased incidence of bleeding and thromboembolic events. This study was undertaken to determine the impact of the late recognition of heparin-induced thrombocytopenia and its sequelae on the morbidity and mortality of open heart surgical patients.

Material and Methods

We conducted a retrospective study to compare the effect of the timing of heparin-dependent antibody (HAAb) diagnosis on morbidity and mortality in patients undergoing open heart operations. Between May 1981 and April 1991, 82 of 4,261 patients (1.9%) undergoing open heart operations were identified to have heparin-induced thrombocytopenia secondary to HAAb. Platelet counts less than 100 × 10^9/L (100,000/µL), new or recurring thromboembolic events, or resistance to heparin therapy prompted suspicion of HAAb. Heparin-platelet aggregation testing was used to confirm the presence of HAAb [7]. The medical records of those patients with positive heparin-platelet aggregation testing were reviewed, and patients were divided into two groups. Group I (n = 12) contained 3 women and 9 men with a median age of 59 years (range, 22 to 78 years) who were diagnosed with HAAb preoperatively. Seven of the 12 patients identified preoperatively received aspirin, dipyridamole, or both as platelet function-inhibiting agents. Group II (n = 70) contained 32 female and 38 male patients with a median age of 68 years (range, 2 to 87 years). Twenty-seven (39%) were receiving aspirin, dipyridamole, or both as a part of their medical management for coronary artery disease preoperatively. Cardiopulmonary bypass was performed with clear prime and moderate systemic hypothermia. All patients had reexposure to heparin at the time of their open heart operation. Only group I patients had total abstinence of heparin after reversal with protamine sulfate. Group II patients had continued exposure to heparin

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Table 1. Coagulation Profile (at lowest platelet count)

Variable	Group I (n = 12)	Group II (n = 70)
Platelets (μL)		
Range	42,000–90,000	11,000–199,000
Median	69,000	46,000
Prothrombin time (s)		
Range	11–18	11–90
Median	14	15
Partial thromboplastin time (s)		
Range	28–47	20–185
Median	31	38
Fibrinogen (mg/dL)		
Range	19–404	36–583
Median	214	176

Table 3. Administration of Blood Products in Patients With Heparin-Dependent Antibody

Product	Group I (n = 12)	Group II (n = 70)
PRBC (units)		
Range	0–19	0–54
Median	4.5	10
FFP (units)		
Range	0–8	0–28
Median	2	5
Cryoprecipitate (units)		
Range	0–1	0–4
Median	0	0
Platelets (6-pack)		
Range	0–2	0–44
Median	0	1

FFP = fresh frozen plasma; PRBC = packed red blood cells.

in monitoring line flushes, heparin-coated flow-directed pulmonary artery catheters, or prophylactic heparinization for devices (eg, intraaortic balloon pump).

Results

Bleeding complications in group I were limited to mediastinal hemorrhage in 3 of 12 (25%). Mediastinal hemorrhage was defined as 200 mL/h or more for at least 3 hours. This required a return to the operating room for mediastinal exploration in 2 patients. There were no thromboembolic events or hospital deaths in group I. Results of coagulation profiles are presented in Table 1.

In group II, 37 of 70 patients (53%) had bleeding complications (Table 2). Eighteen group II patients had mediastinal hemorrhage, and 9 required return to the operating room for mediastinal exploration.

Gastrointestinal bleeding was a particularly serious problem. Twelve patients experienced gastrointestinal bleeding and 6 underwent exploratory laparotomy. Five of the 6 (83%) ultimately died. Laparotomy revealed bleeding duodenal ulcer in 1, perforated ulcer in 1, infarcted sigmoid colon with perforation in 1, colonic bleeding requiring colectomy in 1, and bleeding of undetermined cause in 2 patients undergoing exploratory laparotomy.

The median number of units of packed red blood cells, fresh frozen plasma, and platelets required by group II was greater than twice that required by group I (Table 3).

Thirty-one of 70 group II patients (44%) experienced thromboembolic events: 10 patients had cerebrovascular accident, 13 had lower extremity embolus/thrombosis, 8 had perioperative myocardial infarction, and 6 had pulmonary embolus (Table 4).

Cerebrovascular accidents occurred in 10 (14%) and were associated with death in 4 patients. Of 6 patients who survived after a cerebrovascular accident, 5 required long-term rehabilitation in a specialty facility.

Table 2. Bleeding Complications in Patients With Heparin-Dependent Antibody[a]

Variable	Group I		Group II	
	Complications	Mortality[b]	Complications	Mortality[b]
Mediastinal exploration	2/12 (17)	0/2 (0)	9/70 (13)	3/9 (33)
Gastrointestinal bleeding	0/12 (0)	0/2 (0)	12/70 (17)	5/12 (42)
Mediastinal hemorrhage	3/12 (25)	0/0 (0)	18/70 (26)	8/18 (44)
Pulmonary hemorrhage	0/12 (0)	0/3 (0)	3/70 (4)	2/3 (67)
Epistaxis	0/12 (0)	0/0 (0)	3/70 (4)	0/3 (0)
Cardiac tamponade	0/12 (0)	0/0 (0)	1/70 (1)	1/1 (100)
Hemorrhoidal bleed	0/12 (0)	0/0 (0)	2/70 (3)	0/2 (0)
Flank hematoma	0/12 (0)	0/0 (0)	1/70 (1)	0/1 (0)
CNS bleed	0/12 (0)	0/0 (0)	1/70 (1)	0/1 (0)
Total patients	3/12 (25)	0/3 (0)	37/70 (53)	22/37 (59)

[a] Numbers in parentheses are percentages. [b] Represents mortality in those with bleeding complications.

CNS = central nervous system; group I = patients diagnosed preoperatively; group II = patients diagnosed postoperatively.

Table 4. Thromboembolic Complications in Patients With Heparin-Dependent Antibody[a]

	Group I		Group II	
Variable	Complication	Mortality[b]	Complications	Mortality[b]
Cerebral vascular accident	0/12 (0)	0/0 (0)	10/70 (14)	4/10 (40)
Lower extremity embolus	0/12 (0)	0/0 (0)	13/70 (19)	8/13 (62)
Myocardial infarction	0/12 (0)	0/0 (0)	8/70 (11)	3/8 (38)
Mesenteric thrombus	0/12 (0)	0/0 (0)	3/70 (6)	3/3 (100)
Infarcted spleen	0/12 (0)	0/0 (0)	1/70 (1)	1/1 (100)
Infarcted gallbladder	0/12 (0)	0/0 (0)	1/70 (1)	1/1 (100)
Atrial thrombus	0/12 (0)	0/0 (0)	1/70 (1)	1/1 (100)
Mitral valve thrombus	0/12 (0)	0/0 (0)	1/70 (1)	0/1 (0)
Ventricular thrombus	0/12 (0)	0/0 (0)	1/70 (1)	0/1 (0)
Coronary artery thrombus	0/12 (0)	0/0 (0)	1/70 (1)	0/1 (0)
Phlebitis	0/12 (0)	0/0 (0)	1/70 (1)	0/1 (0)
Renal mural thrombus	0/12 (0)	0/0 (0)	1/70 (1)	0/1 (0)
Thrombus in aorta	0/12 (0)	0/0 (0)	1/70 (1)	0/1 (0)
Pulmonary embolus	0/12 (0)	0/0 (0)	6/70 (9)	3/6 (50)
Total patients	0/12 (0)	0/0 (0)	31/70 (44)	14/31 (45)

[a] Numbers in parentheses are percentages. [b] Represents mortality in those with thromboembolic complications.

CNS = central nervous system; group I = patients diagnosed preoperatively; group II = patients diagnosed postoperatively.

One patient required operation for removal of an aortic thrombus. This patient survived hospitalization. Lower extremity arterial embolus or thrombosis was associated with amputation in 2 patients, vascular bypass in 2 patients, and fasciotomy in 2 patients. Four of the 6 who required operation for lower extremity ischemia died in the hospital.

The etiology of myocardial infarctions was undetermined. However, the incidence was 11% in group II, whereas none occurred in group I.

Pulmonary embolus was associated with hospital death in 3 of 6 patients (50%). Two of these patients required emergency operation for pulmonary embolectomy (1 hospital death).

Renal failure requiring dialysis occurred in 21 of 70 patients (30%). This was a particularly common finding in those who died (19/23; 83%). However, it was undetermined if the renal failure was a result of a culmination of multisystem failure or an embolic phenomenon. Pulmonary hemorrhage was also a late complication and was associated with multisystem failure.

Twenty-three of 70 group II patients (33%) died in the hospital. The median number of packed red blood cells required by these patients who died was 16 units (range, 3 to 54 units). The amount of platelets required by these patients (median, 3 units; range, 0 to 44 units) was three times greater than that of all patients in group II. These patients also required more fresh frozen plasma (median, 7 units; range, 0 to 24 units) than other group II patients. Death was associated with renal failure requiring dialysis in 19, cerebrovascular accident in 3, pulmonary embolus in 3, and an ischemic extremity requiring an operation in 4 patients.

Comment

Delayed heparin antibody-induced thrombocytopenia was clearly recognized as an entity in 1973 [4]. It may occur from 4 to 15 days after initial heparin exposure and its occurrence is independent of dose, route, and type of heparin. The incidence has been reported from 0.4% to 31% [8]. Those with reexposure to heparin may have development of thrombocytopenia earlier (range, 1 to 9 days; mean, 5 days) [9]. Chronic exposure to heparin perpetuates the ongoing platelet aggregation. We found in this series that it was possible to undergo cardiopulmonary bypass using heparin without serious thromboembolic events if all sources of heparin were avoided postoperatively.

The incidence of HAAb in this series of open heart surgical patients was 1.9%. The occurrence of HAAb in open heart surgical patients is probably greater because all patients did not have testing for the presence of the heparin antibody. Prospective studies are necessary to define the true incidence of HAAb in open heart surgical patients. Once the true incidence is determined, then recommendations can be made regarding routine screening.

Open heart operation with pretreatment using platelet function-inhibiting agents (aspirin or dipyridamole) before heparinization, a clear pump prime for cardiopulmonary bypass with moderate systemic hypothermia, and avoidance of all forms of heparin postoperatively has been performed without the development of thromboembolism [6, 10]. Platelet function-inhibiting agents can reduce the aggregation of platelets, which may lead to bleeding or thromboembolic sequelae. A clear pump prime and moderate systemic hypothermia during cardiopulmonary by-

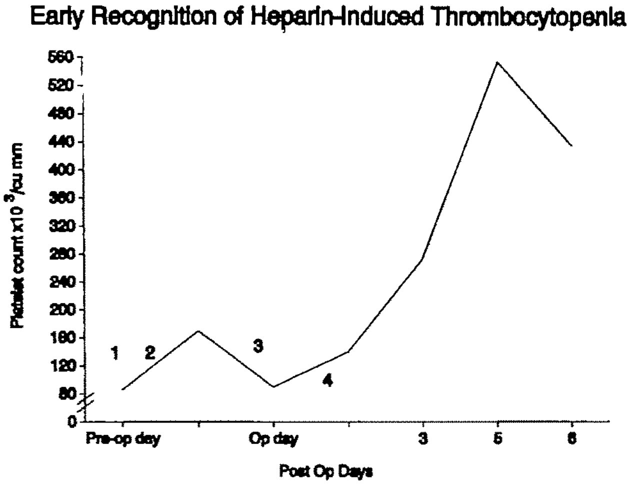

Fig 1. A 62-year-old man with recent myocardial infarction received a heparin drip (1). Thrombocytopenia developed, and heparin-dependent antibody testing was positive (2). Heparin administration was discontinued and aspirin therapy initiated before cardiopulmonary bypass (3). After quintuple coronary artery revascularization and mitral valve replacement, all sources of heparin were avoided (4), the thrombocytopenia resolved, and the patient experienced no bleeding or thromboembolic complications.

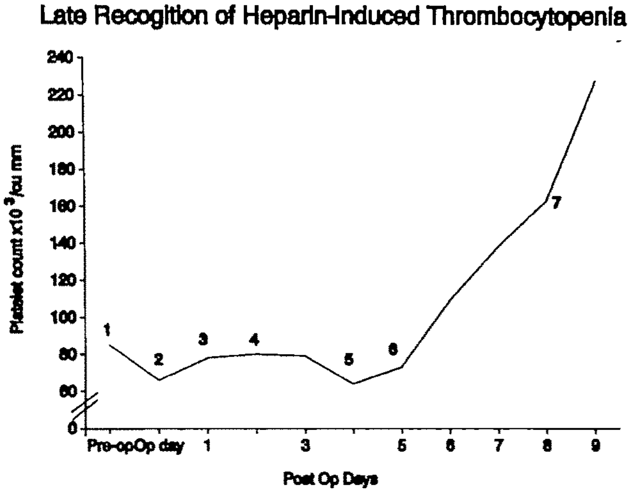

Fig 2. A 57-year-old woman had quadruple coronary artery revascularization (1). After cardiopulmonary bypass she had thrombocytopenia (2). On the first postoperative day she was obtunded and computed tomographic scan of the head showed multiple cerebral infarcts (3). She experienced mediastinal hemorrhage requiring a return to the operating room (3). Due to a suspected lower extremity embolus, heparin therapy was started on postoperative day 2 (4). The platelet count decreased further and a pulseless lower extremity required right femoral embolectomy and fasciotomy on day 4 (5). Heparin administration was discontinued and thrombocytopenia resolved (6). Heparin-dependent antibody testing was positive on day 8 (7), and no further heparin was given. A protracted recovery resulted in dismissal on the 37th postoperative day.

pass may reduce the concentration of blood elements and immunologic reaction, thus reducing platelet aggregation.

Early recognition of heparin antibody and cessation of all forms of heparin can reduce morbidity and mortality (Fig 1) [1, 5–7]. Even heparin-coated pulmonary artery flow-directed catheters have been associated with heparin-induced thrombocytopenia [11]. Use of heparin for diagnostic and therapeutic procedures, intravascular line flushes, and heparin-bonded devices in patients with heparin antibody may cause heparin-induced thrombocytopenia coagulation disorders [12].

In this study all 12 patients with known HAAb preoperatively had development of thrombocytopenia postoperatively. Two required mediastinal exploration for mediastinal hemorrhage. Five patients who were treated only by avoidance of heparin postoperatively (without pretreatment with antiplatelet drugs) had no thromboembolic events.

In contrast to preoperative diagnosis, postoperative diagnosis (group II) was associated with an increased incidence of bleeding and thromboembolic sequelae which increased morbidity and mortality (Fig 2). Although bleeding or thromboembolic complications occurred at a median of 1 day postoperatively, the diagnosis of HAAb was not made until a median of 6 days postoperatively. Shed blood from mediastinal chest tubes was excessive in more than 25% of the group II patients. Return to the operating room for mediastinal exploration was three times our usual incidence of 3.9%.

In conclusion, this study emphasizes the serious nature of heparin antibody in patients requiring open heart operations. Recognition of HAAb preoperatively and pretreatment with platelet function-inhibiting agents (aspirin, dipyridamole, or both) before heparinization for cardiopulmonary bypass is recommended. Use of a clear pump prime and moderate systemic hypothermia during cardiopulmonary bypass may be helpful. Patients undiagnosed preoperatively who have thromboembolism, development of heparin resistance, or platelet counts less than 100 × 10^9/L (100,000/μL) should have platelet aggregation testing. If the test is initially negative, it should be repeated again after cessation of all heparin for 24 hours. In the presence of HAAb, strict avoidance of all sources of heparin after cardiopulmonary bypass is mandatory to reduce morbidity and mortality.

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DISCUSSION

DR ROBERT M. SADE (Charleston, SC): I think this is a very important contribution. Most of us have seen problems from this particular entity, but it does not happen often enough to be in the front of our minds all the time. It needs to be, particularly when a patient has a low platelet count after an open heart operation.

DR WILLIAM H. COLTHARP (Nashville, TN): I would like to congratulate Dr Walls on this discussion. Our most recent experience with this was in a 39-year-old man who, 3 days before we saw him, was seen at an outside hospital with an acute anterior myocardial infarction. He received streptokinase and was put on heparin at that time. He was catheterized and had a 99% proximal anterior descending lesion, and he was transferred to our hospital for operation. His platelet count had fallen from 220×10^9/L to 65×10^9/L (220,000/μL to 65,000/μL) upon admission to our hospital, and we diagnosed, with the help of the hematologist, this syndrome in that patient. We elected to try to postpone his operation until his platelet count came back to a reasonable level; however, his condition became unstable that night and necessitated operation in the face of that thrombocytopenia.

My question for you is, when it is diagnosed preoperatively, what platelet count do you try to achieve before operation? Do you have any alternative other than operating on those patients in unstable condition with thrombocytopenia?

DR WALLS: When heparin antibody is diagnosed, all sources of heparin should be discontinued. If the patient's hematologic system can recover a few days until a platelet count greater than 100×10^9/L (100,000/μL) is reached, the risk of bleeding complications may be reduced. Heparin antibody may be present in the patient for greater than a year; therefore, a critically ill cardiac patient requiring open heart operation may not be able to be postponed.

DR RICHARD E. CLARK (Pittsburgh, PA): What is the role of plasmapheresis used preoperatively in these patients who have severe antibody reactions? We have used plasmapheresis and steroids, and delayed operation for 3 months. When retested, the patients remain sensitive to heparin.

We have had some experience with Iloprost. It must be used cautiously because it is a synthetic prostaglandin I_2 and causes hypotension. However, heparin is not required. I am surprised that you give heparin before cardiopulmonary bypass. Did the platelet count decrease to markedly low levels? Were the platelet counts different between the two groups of patients in your study before or after cardiopulmonary bypass?

I bring to the Association's attention another antibody that has developed after cardiac operations. It is an antibody to bovine thrombin. We have had 8 patients in the last year who had previous cardiac operations and required reoperation in which bovine thrombin was used. Three patients had development of delayed bleeding in the gut, in the pericardium, and in the brain. Have you been able to identify anything like that in your practice?

DR WALLS: We have not identified antibody to bovine thrombin in any of our patients. Also, we have not used plasmapheresis in this particular group of patients. In group I (those patients diagnosed preoperatively), the median platelet count was 46×10^9/L (46,000/μL). In group II patients (those diagnosed postoperatively), the median platelet count was 68×10^9/L (68,000/μL). I believe that one point to be clearly emphasized is do not give heparin in any form postoperatively to patients with known heparin antibody.

The Influence of Age and Sex on Human Internal Mammary Artery Size and Reactivity

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Harry A. Lutz III, PhD, and Andrew S. Wechsler, MD

Department of Surgery, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

Internal mammary arteries (IMAs) from women and the elderly have been postulated to be smaller and more reactive than IMAs from men and younger patients and, therefore, not as reliable for coronary artery bypass grafting in the short term. This study tests the physiologic basis for that hypothesis. Trimmed IMA segments were obtained from patients aged 50 to 76 years at coronary artery bypass grafting. Eighteen ring segments from 12 women and 35 ring segments from 17 men were mounted on a strain-gauge apparatus, and internal diameter at a transmural pressure of 100 mm Hg was determined from length-tension curves. Contractions to potassium chloride and a dose-response curve to norepinephrine or serotonin were obtained to simulate physiologic vasospasm. Sodium nitroprusside determined arterial relaxation. Linear regression was used to determine correlation of these parameters with age. Internal mammary arteries from women and men were of equal size. They had equal strength of contraction to potassium chloride and norepinephrine, but female IMAs had greater strength of contraction to serotonin. Female IMAs had weaker contraction to norepinephrine as a percent of maximum contraction to potassium chloride than IMAs from men. Internal mammary arteries from women had equal relaxation to sodium nitroprusside compared with IMAs from men. There was no correlation between age and arterial reactivity to vasoconstrictors, relaxation to sodium nitroprusside, or size. These data suggest that IMAs from women and the elderly are not more susceptible to reduction in flow due to smaller size. Postoperatively, it may be important that women be kept on platelet inhibitors because of their greater absolute contraction to serotonin and men on nitrovasodilators because of their greater relative contraction to norepinephrine.

(Ann Thorac Surg 1992;53:792–7)

The internal mammary artery has been shown to be an excellent conduit for coronary artery bypass grafting. The need for arterial revascularization has increased in women and the elderly as the frequency of coronary bypass grafting in these patients has increased. Internal mammary arteries from women and the elderly are thought to be smaller and more reactive than those from men and younger patients and, therefore, not as reliable for coronary artery bypass grafting in the short term. This becomes of particular importance when inotropic agents that possess α-adrenergic properties are required or during hypotension when neurogenic catecholamine release may occur. Frequency of vasospasm has not been tested in these subgroups. Comparison of arterial reactivity to vasoconstrictor substances such as circulating catecholamines and platelet products is important in understanding and preventing graft spasm. Canine and human internal mammary artery reactivity to various constrictor and dilator substances has been studied in the context of coronary artery bypass grafting [1–3], but little is known about differences between male and female arteries and those of older patients. This study tested the hypothesis that internal mammary arteries from women and elderly patients are smaller and more reactive than internal mammary arteries from men and younger patients. A common vasoconstrictor circulating perioperatively, norepinephrine, and a product of platelet aggregation, serotonin, were chosen to initiate humoral, physiologic contraction. Potassium chloride was used to obtain maximum smooth muscle contraction. Vascular dilation was assessed using sodium nitroprusside because of its direct, smooth muscle action and its frequent perioperative use.

Material and Methods

Trimmed internal mammary artery segments (n = 53) were obtained from 12 women and 17 men between the ages of 50 and 76 years (men, 60.0 ± 2.2 years; women, 66.1 ± 2.0 years [not significant]) at coronary artery bypass operation. (This protocol was approved by the institutional committee on the conduct of human research and all patients gave informed consent.) The specimens were kept in iced, physiologic saline solution until studied. The solution had the following composition (in millimoles per liter): NaCl, 119; KCl, 4.6; $CaCl_2$, 2.5; $MgSO_4$, 1.17; $NaHCO_3$, 25; KH_2PO_4, 1.17; EDTA, 0.027; and glucose, 11. (All chemicals were obtained from Sigma Chemical Company, St. Louis, MO.) A ring segment 3 mm in length was prepared by a transverse cut with a razor blade and mounted on two stainless steel wires in a

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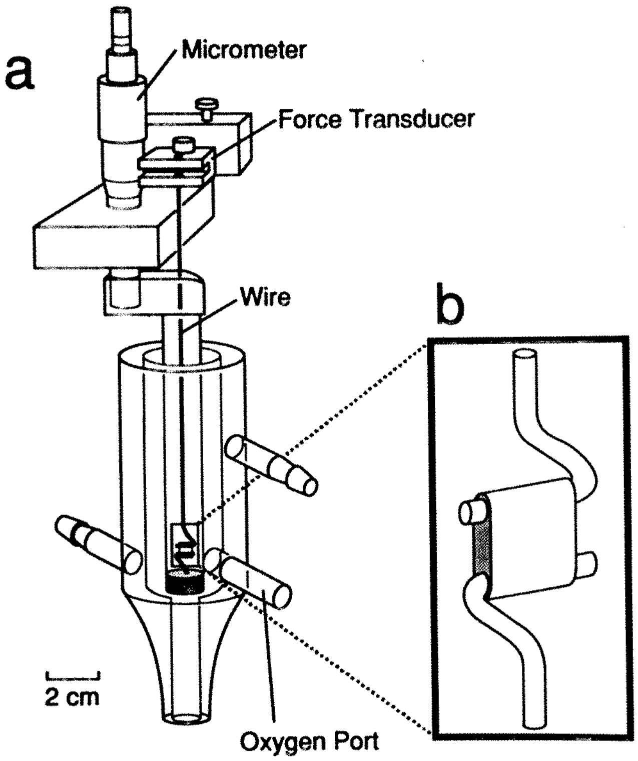


Fig 1. (a) Organ bath with strain-gauge transducer. (b) Arterial ring segment mounted on wire hooks. (Reprinted from Dignan RJ, Yeh T Jr, Dyke CM, et al. Reactivity of gastroepiploic and internal mammary arteries. Relevance to coronary artery bypass grafting. J Thorac Cardiovasc Surg 1992;103:116–23, by permission of Mosby-Year Book, Inc.)

6-mL water-jacketed glass organ bath (Fig 1). The upper wire was attached to a Grass FT03D force transducer (Grass Instrument Company, Quincy, MA). The lower wire was fixed to a micrometer (Mitutyo, Tokyo, Japan). Ring segments were allowed to relax in the organ bath in oxygenated (95% oxygen, 5% carbon dioxide), normothermic, buffered saline solution for 60 minutes.

A wide range of diameters was observed in the vessels obtained. Therefore, a normalization procedure was performed to standardize baseline resting length at which subsequent tension measurements were to be obtained. This method has been previously described for small [4] and large arteries and large veins [1, 5]. The normalization procedure predicted the circumference of each vessel at a pressure of 100 mm Hg (L_{100}), allowing all arteries to be studied at comparable resting conditions.

Passive length-tension curves were obtained for each vessel by sequentially separating the wires using a micrometer. Force generated by the vessel was recorded on a Grass Model 7 Polygraph and the micrometer setting noted at each step. Vessel tension (T) was calculated at each step from the equation

$$T = \text{Force}/2g$$

where g is the length of the segment. Internal circumference (L) was determined from the equation

$$L = (\pi + 2)d + 2f$$

where d is the wire diameter and f is the distance between the wires. To ensure that the vessel was not overstretched, pressure was calculated from the tension and internal circumference after each step. When pressure was greater than 100 mm Hg, vessel stretch was released. Nonlinear regression was used to obtain the best exponential fit of the length-tension curve. A line was generated by solving the Laplace formula ($P = 2\pi T/L$) for tension, assuming a pressure equal to 100 mm Hg

$$T = (100 \text{ mm Hg})L/2\pi$$

and plotting the tensions on the isobaric line against the internal circumference. A personal computer–based program [6] modified in our laboratory was used to determine the intersection of the length-tension curve and the line by an iterative fitting technique (Fig 2). This intersection determined the internal circumference (L) the vessel was predicted to have at a transmural pressure of 100 mm Hg and is called L_{100}.

The internal circumference of every vessel was set at 90% of L_{100} (L_{90}). The isometric force at this setting is the "passive" or "resting" force in the absence of constrictor tone. This method of determining resting force allows maximum tension development [7] while standardizing resting tension independent from vessel diameter. Passive resting force was therefore determined for each vessel from its length-tension curve and not by nonspecific methods that have frequently been used in similar studies using isolated vessel rings.

Arterial segments were allowed to equilibrate for 15 to 20 minutes at L_{90} before proceeding (Fig 3). They were contracted twice using 125 mmol/L potassium chloride, rinsed, and allowed to equilibrate before and after the second contraction. Concentration-response curves were obtained (one per ring segment) to norepinephrine (10^{-9}

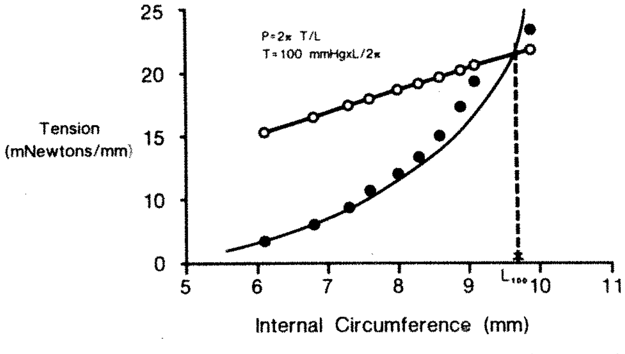


Fig 2. Normalization procedure for one arterial segment. The curved line *represents the experimentally determined length-tension relationship of one vessel. It was obtained by progressively stretching the ring segment and plotting tension measurements as a function of internal circumference. The best exponential fit was obtained using nonlinear regression.* The straight line *is the mathematical solution of the Laplace relation where pressure is equal to 100 mm Hg. The intersection of the curve and the line determined the internal circumference the vessel would have at a transmural pressure of 100 mm Hg* (L_{100}). *(P = pressure; T = tension.)*

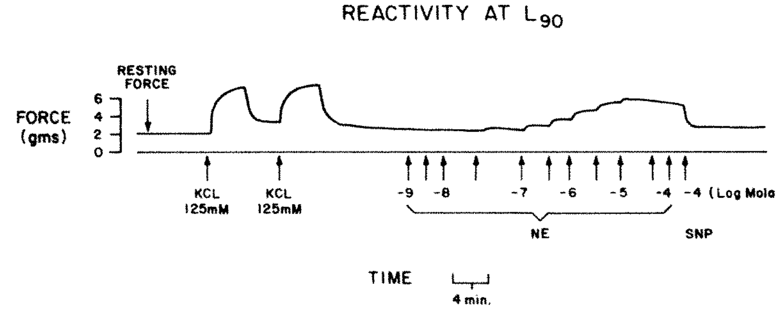


Fig 3. The conduct of the experiment is illustrated in this tracing of the force generated by a typical ring segment. The ring was contracted twice using 125 mmol/L potassium chloride (KCL). Half-log molar concentrations of norepinephrine (NE) starting at 10^{-9} mol/L and ending at 10^{-4} mol/L were used to obtain a concentration-response curve. The ring was relaxed with sodium nitroprusside (SNP).

to 10^{-4} mol/L) or serotonin (10^{-9} to 10^{-4} mol/L). Drug concentrations used started below threshold and ended when maximum contraction was achieved. Maximum smooth muscle relaxation was measured using sodium nitroprusside (10^{-4} mol/L) (see Fig 3).

Tension at L_{90} was converted to pressure using the Laplace relationship ($P = 2\pi T/L_{90}$). All ring segments studied were included in the statistical analysis.

Two measurements quantified arterial ring segment reactivity: maximum contraction and sensitivity (Fig 4). Maximum mean contraction was calculated for each constrictor and compared between and within groups of arteries. Norepinephrine and serotonin contractions were also compared as percent of maximum potassium contraction. Sensitivity was measured by effective drug concentration producing 50% of maximum contraction (EC_{50}), which was calculated from concentration-response curves generated by a symmetric sigmoidal curve model for every ring segment using personal computer-based software. Average EC_{50}s for each constrictor were compared between groups. Mean concentration-response curves to serotonin and norepinephrine for each group of vessels were generated using mean pressures at each concentration of serotonin and norepinephrine. Relaxation to sodium nitroprusside was expressed as a percent of contraction to the drug used. The comparisons were subject to analysis of variance, accepting a value of p less than 0.05 as significant. Regression analysis was used to test the correlation of age with seven variables: diameter; maximum contraction to potassium, norepinephrine, and serotonin; EC_{50} of norepinephrine and serotonin, and relaxation to sodium nitroprusside.

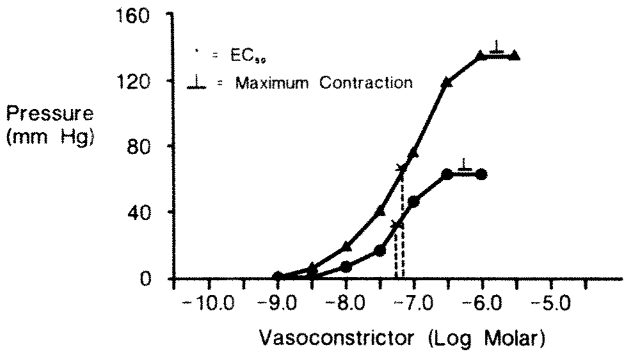


Fig 4. Two measurements quantified arterial ring segment reactivity. Maximum contraction was the highest pressure generated by each vasoconstrictor. Sensitivity was determined by effective concentration producing 50% of maximum contraction (EC_{50}). Symmetric sigmoidal curves generated for two ring segments are pictured here. The EC_{50} for the two rings is very similar but the maximum contraction is significantly different.

Results

Sex Differences

SIZE. The diameters of the ring segments from men and women, as determined by L_{100}, were not significantly different (1.76 ± 0.10 versus 1.60 ± 0.06 mm, respectively).

ARTERIAL CONTRACTIONS. Internal mammary arteries from women had equal strength of contraction to potassium (115 ± 13 versus 103 ± 6 mm Hg) and norepinephrine (96 ± 7 versus 112 ± 4 mm Hg) but greater strength of contraction to serotonin (71 ± 15 versus 26 ± 3 mm Hg) compared with internal mammary arteries from men (Fig 5a). Both internal mammary arteries had similar contractions to potassium and norepinephrine. Male internal mammary arteries had significantly weaker contractions to serotonin than to norepinephrine or potassium (see Fig 5a). Female internal mammary arteries, however, had equal contractions to serotonin and norepinephrine. Female internal mammary arteries had weaker contraction to norepinephrine (82% ± 9% versus 113% ± 9%) as a percent of maximum potassium contraction than the internal mammary arteries from men (Fig 5b).

ARTERIAL SENSITIVITY. Concentration-response curves to norepinephrine and serotonin (Figs 6, 7) were located in the same position on the horizontal axis for both internal mammary arteries. The calculated EC_{50}s of serotonin ($1.2 \pm 0.4 \times 10^{-7}$ versus $1.5 \pm 0.2 \times 10^{-7}$ mol/L) and norepinephrine ($0.63 \pm 0.02 \times 10^{-7}$ versus $1.30 \pm 0.2 \times 10^{-7}$ mol/L) were equal in female and male internal mammary arteries, indicating equal sensitivity of the arteries to those drugs. There was a significant difference in the upper portion of the serotonin curve, however, because the strength of contraction was greater in the female internal mammary arteries (see Figs 6, 7).

ARTERIAL RELAXATION. The vessels had no significant difference in relaxation to sodium nitroprusside (female, 132.6% ± 14.1%; male, 117.2% ± 8.1%).

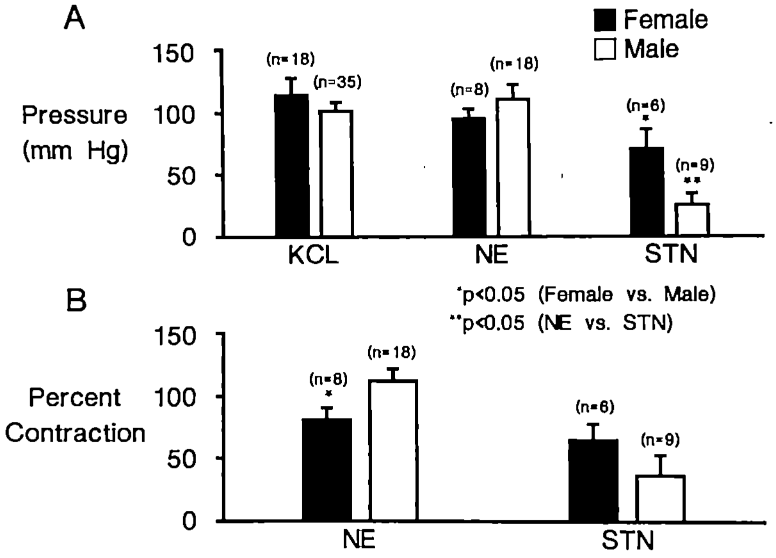


Fig 5. (A) Contractile function to potassium chloride (KCL), norepinephrine (NE), and serotonin (STN) is demonstrated for female and male internal mammary arteries. Strength of contraction to KCL and NE were equal, but contraction to STN was significantly greater in the female internal mammary arteries. Female internal mammary arteries had similar contractions to KCL, NE, and STN. Male internal mammary arteries had significantly weaker contractions to STN than to NE or KCL (indicated with double asterisks*). (B) Norepinephrine and STN contractions were normalized to the KCL contractions by calculating them as percent of KCL contraction, as is frequently done by other authors when diameter and, therefore, pressure are unknown. There is no significant difference in contraction to STN. Male internal mammary arteries, however, had significantly weaker contractions to NE as a percent of KCL contraction.*

Age Differences

There was no linear correlation, as determined by the r^2 coefficient, between age and measurements of sensitivity, maximum contraction to potassium, norepinephrine, and serotonin, or relaxation to nitroprusside (Table 1). Plots of age versus maximum contraction to potassium, serotonin, or norepinephrine or EC_{50} of norepinephrine or serotonin were scattered, as were those of age versus relaxation to sodium nitroprusside (Fig 8). The L_{100} was not significantly different as age increased. There was also no correlation between any of the variables and age when female or male subgroups were analyzed.

Comment

This study shows equal size, equal sensitivity to norepinephrine and serotonin, equal maximum contraction to potassium and norepinephrine, and equal relative contraction to serotonin of internal mammary arteries from men and women. The maximum contraction to serotonin and relative contraction to norepinephrine, however, are different. Serotonin is thought to cause coronary artery vasospasm [8]. It is also known to cause contraction in the human internal mammary artery [9, 10] and is likely to cause vasospasm in the internal mammary artery as well. Although the difference in reactivity of female and male internal mammary arteries to serotonin shown in this study has not been previously studied, the literature suggests interaction between estrogen and serotonin receptors. Serotonin interacts with specific serotonin receptors, probably the S_2 subtype, on vascular smooth muscle [11, 12]. Estradiol increases serotonin receptor binding in rats [13] and also induces uterine sensitivity to serotonin (S_2-receptor mediated) [14]. This estrogen and S_2-receptor

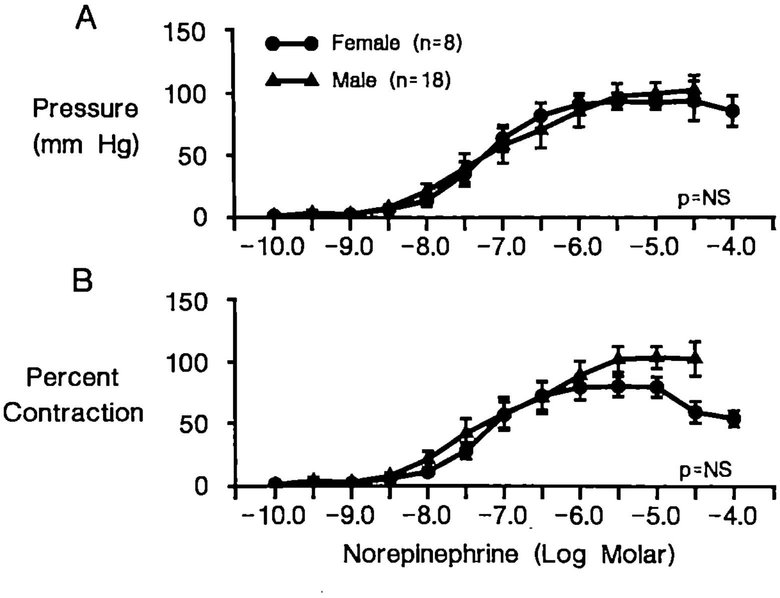
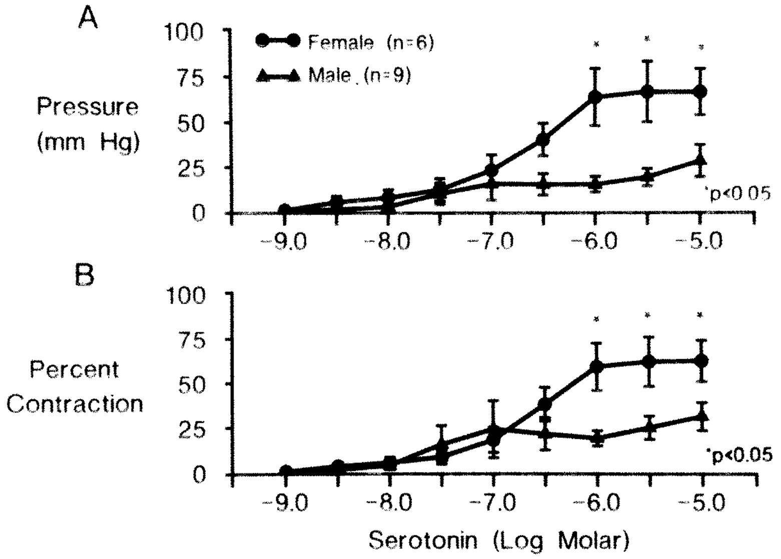


Fig 6. Concentration-response curves to norepinephrine for female and male internal mammary arteries. (A) The curves are located at the same position on the horizontal axis, demonstrating that the effective concentration producing 50% contraction and, therefore, sensitivity to norepinephrine was equivalent in both groups. (B) When mean contractions at specific concentrations are normalized to potassium chloride contractions, there is no difference in strength of contraction to norepinephrine. (NS = not significant.)

Fig 7. Concentration-response curves to serotonin for internal mammary arteries. (A) The curves are located at the same place on the horizontal axis, showing that the effective concentration producing 50% contraction and therefore sensitivity to serotonin was equal in female and male internal mammary arteries. (B) Mean maximum contraction and contraction as percent of potassium contraction for the highest three concentrations of serotonin for female internal mammary arteries is greater than for male internal mammary arteries.



interaction may be the mechanism for greater contraction to serotonin in internal mammary arteries from women. Further studies are required to verify this.

Many patients undergoing coronary bypass are given platelet inhibitors. In this study, 10 women (55%) and 13 men (37%) were taking aspirin at the time of operation. Platelet inhibitors such as aspirin are known to inhibit the release of products of arachidonic acid metabolism. In one study, however, pretreatment of arteries with aspirin did not affect the contractile responses of rabbit coronary arteries and aorta to platelets [15]. The relation between internal mammary artery reactivity and aspirin ingestion was analyzed by comparing reactivity and relaxation of internal mammary arteries from patients receiving aspirin and those not receiving aspirin. There was no difference in any of the variables of any of the vasoconstrictors (potassium, norepinephrine, or serotonin). There was no difference in contraction to potassium in either men given aspirin or women given aspirin compared with those not given aspirin. Numbers were inadequate to compare reactivity to norepinephrine or serotonin of female and male internal mammary subgroups receiving aspirin.

Studies on aortic and large artery stiffness [16] show a progressive stiffening due to structural changes in the seventh decade. There is a lower degree of stiffness in women until menopause, after which they show an accelerated stiffening equal to men in the seventh decade. Compliance factors were not analyzed in this study but may contribute to differences in reactivity in internal mammary arteries from men and women at a younger age.

This study showed no correlation between age and reactivity. Studies in rats have suggested that serotonin response increases with age in coronary resistance arteries [17]. This effect was not demonstrated in this study, possibly due to low numbers or because the ring segments were taken from large arteries rather than resistance vessels.

A well-known age-dependent change in vascular reactivity is the disappearance of β-receptor–mediated relaxation of rabbit and rat aorta [18]. Increasing contraction to norepinephrine with age, if demonstrated in this study, would have indicated possible decrease in number of β-receptors with age. Human internal mammary artery, however, has been shown to have only a few β-receptors. Adenosine-mediated vasodilatation diminishes with age also, indicating a general loss of vasodilator potential in the aorta with age [19]. Although vasoconstrictor responses to potassium, norepinephrine, and serotonin increase in small animal aorta in the early part of life [20], in the later part, they decrease [19]. This does not appear to be true in human internal mammary artery, where there appears to be no change in contraction or relaxation with age.

In conclusion, internal mammary arteries from women and the elderly are not more susceptible to reduction in flow due to size. The use of platelet inhibitors may be more important in women because of greater contraction to serotonin and nitrovasodilators in men because of greater relative contraction to norepinephrine in the perioperative interval when the internal mammary artery is

Table 1. Influence of Age on Internal Mammary Artery Size and Reactivity[a]

Variable	Total Group	Female	Male
I_{100}	0.09	0.01	0.01
KCl contraction	0.17	0.18	0.14
NE contraction	0.009	0.25	0.009
STN contraction	0.05	0.03	0.28
SNP relaxation	0.18	0.34	0.003

[a] Regression analysis: numbers represent r^2 values for correlation between age and variables. (p = not significant.)

KCl = potassium chloride; I_{100} = internal circumference at 100 mm Hg; NE = norepinephrine; SNP = sodium nitroprusside; STN = serotonin.

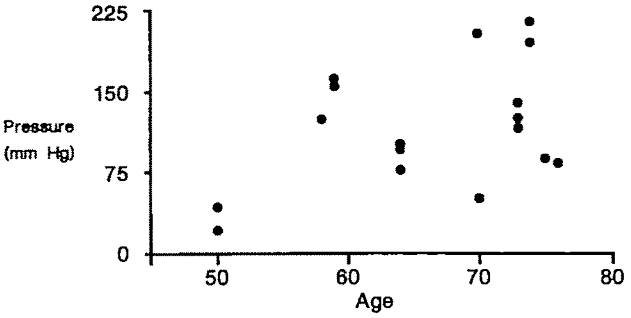


Fig 8. Plots of age versus maximum contraction to potassium of the female internal mammary artery were scattered, as were those of age versus every variable in the combined female and male group and in subgroups.

used for coronary artery bypass operation. Obviously, further pharmacologic studies of receptor differences are required. Better understanding of physiologic peculiarities of the internal mammary artery may influence short-term perioperative management.

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DISCUSSION

DR TIMOTHY J. GARDNER (Baltimore, MD): That was a nice presentation. I think that it emphasizes a point that we made based on a clinical series a couple of years ago that the internal mammary artery is quite suitable for use in elderly patients and also in women. In fact, not only is the internal mammary artery probably no different anatomically or physiologically, but when compared with available vein conduits in elderly women, it may in fact be superior.

One clinical point that we have noticed in elderly patients more often than in younger patients and in females more often than in males is that the distal internal mammary artery, after having been infused with papaverine, appears to be more friable and susceptible to dissection of the vessel wall. This may be a point of some technical importance, because if you have a partially dissected or friable mammary tip and your sutures include only the outer wall of the artery, the inner wall can telescope backward and result in an obstruction.

DR DIGNAN: Thank you for that comment. We do not have data to support or disprove your experience. In elderly patients one would expect more atherosclerosis, which might contribute to dissection. Internal mammary arteries, however, have been shown to develop atherosclerosis infrequently.

DR FREDERICK L. GROVER (Denver, CO): Did you correlate reactivity with diabetes?

DR DIGNAN: No, we did not correlate reactivity with diabetes. We have information as to which patients were receiving insulin, however. A study comparing internal mammary artery reactivity of patients receiving insulin with that of those not receiving insulin would be interesting.

Esophageal Reconstruction for Esophageal Strictures or Resection After Corrosive Injury

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A total of 75 esophageal reconstructions were performed for caustic esophageal strictures (65 patients) or postcaustic resection (10 patients) at Naval General Hospital and National Cheng-Kung University Hospital from September 1976 to April 1991. Reconstructive procedures included bypass in 61 patients, replacement of the esophagus through the substernal route in 10, and replacement of the esophagus through the posterior mediastinum in 4. Esophageal substitutes used for reconstruction were a long segment of the ileum and the ascending colon in 42 patients; a short segment of the ileum and the ascending colon in 18; the ascending colon and transverse colon in 3; the ascending, transverse, and left colon in 1; the transverse and left colon in 6; the jejunum in 2; and the stomach in 3. All but two of the esophageal substitutes were isoperistaltic. There were 28 postoperative complications in 24 (32%) of the 75 patients. Cervical anastomotic leakage occurred in 5 patients (6.7%). There were no operative deaths. Postoperatively, swallow function was considered good in 67 patients (89.3%). In this experience, isoperistaltic transposition of the transverse and left colon provided the best results.

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The ingestion of a corrosive agent is not rare and usually occurs among adults as an intentional suicide attempt [1, 2]. In Taiwan most caustic accidents involve acids, which cause more damage to the stomach than to the esophagus. In acid-injured patients with antral strictures only, surgical intervention on the stomach is sufficient. However, in the case of severe caustic esophageal strictures, an esophageal reconstructive operation is necessary [1–20]. In most of our esophageal reconstructive procedures, we use the right ileocolon as the esophageal substitute. The stomach of a lye-injured patient can be used as an alternative esophageal substitute if it has not sustained corrosive injury. In an acid-injured patient whose right ileocolon lacked an adequate blood supply, the jejunum was used as an esophageal substitute. Lately, we have chosen the transverse and left colon as the esophageal substitute.

We evaluated the results of use of different esophageal substitutes. Here we report our experience during the past 15 years with reconstructive operation as treatment of caustic strictures and of postcaustic resections of the esophagus injured by various agents. The clinical data, the severity of the strictures, the technical considerations, and the long-term results are discussed.

Material and Methods

From September 1976 to April 1991, a total of 75 consecutive patients with severe caustic esophageal strictures (65 patients) or postcaustic resection (10 patients) were treated at Naval General Hospital and National Cheng-Kung University Hospital. All underwent esophageal reconstruction by us. The medical records, initial management, operative data, postoperative course, and follow-up data were reviewed. Patients with caustic strictures who did not require or refused esophageal reconstruction and patients with esophageal stricture resulting from other causes were excluded from this study.

There were 23 male and 52 female patients ranging in age from 2 to 62 years (average age, 27 years). Hydrochloric acid was the most frequently ingested agent (n = 52 patients, 69.3%), followed by alkaline substances (n = 15, 20%) and other substances (n = 8, 10.7%). The intent to commit suicide was the motivation for all the adult patients (n = 62); in the children (n = 13), the ingestion was accidental. The interval between ingestion of the caustic agent and the reconstructive procedure ranged from 2 months to 15 years. Thirty-three patients (44%) were operated on within 6 months after injury and the others, after longer intervals: 10 patients after 6 months to 1 year; 19 patients after 1 year to 3 years; 5 patients after 3 to 5 years; and 8 patients after 5 to 15 years.

Fifty-seven (87.7%) of the 65 patients with severe esophageal strictures were referred to us from other hospitals for surgical reconstruction of the esophagus. Of these patients, 14 (21.5% of all patients with stricture) had undergone weekly wire-guided bougienage of the esophagus for varying periods, but this had failed. The remaining patients had not undergone dilation before esophageal reconstruction. Eighteen patients were initially treated in our hospitals after corrosive injury. The initial treatment of acute cases included nasogastric decompression, correction of the acid-base imbalance, antibiotics, and ventilatory assistance, with or without emergency

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Table 1. Level of Esophageal Strictures and Postcaustic Resection in 75 Patients[a,b]

Variable	No. of Patients
Stricture level	
Hypopharynx	11 (14.7)
Cervical esophagus	12 (16)
Thoracic esophagus	42 (56)
Status after esophagogastrectomy	9 (12)[c]
Status after esophagogastroduodenectomy + partial jejunectomy	1 (1.3)[d]

[a] Most patients had multiple esophageal strictures. [b] Numbers in parentheses are percentages. [c] Three patients had complete obstruction of esophageal orifice after esophagostomy. [d] Patient had complete obstruction of esophageal orifice after esophagostomy.

surgical intervention. Nine patients underwent emergency esophagogastrectomy and 1 patient, esophagogastroduodenectomy plus a partial jejunectomy. In a patient with a chronic condition, the reconstructive procedures were performed after psychological stabilization.

Most patients had multiple esophageal strictures. The patients are classified by type of upper-level stricture in Table 1. Associated caustic sequelae included gastric strictures (28 patients), esophagorespiratory fistula (2 patients), laryngeal stricture (3 patients), and tracheal stenosis (1 patient).

The indications for reconstruction of the esophagus include complete obstruction of the esophagus or narrowing of the lumen until it permits passage of only liquid, or strictures secondary to postcaustic resection of the esophagus. Preoperative evaluation of the level of stricture is essential. It was done by esophagography and esophagoscopy. Preoperative preparation of the colon consisted of the administration of enemas on 2 consecutive days and three doses of erythromycin and neomycin sulfate. In some instances, intraoperative endoscopy was used to confirm the patency of the reconstructed alimentary tract.

Operative procedures included bypass in 61 patients, replacement of the esophagus through the substernal route in 10, and replacement of the esophagus through the posterior mediastinum in 4 (Table 2). The types of esophageal substitutes used are shown in Table 3. All but two of the esophageal substitutes were isoperistaltic. Temporary tracheostomy was performed in 3 patients, and a tracheal stent was placed in 1 patient to maintain upper airway patency.

Technical Considerations

After esophagogastrectomy, substernal replacement of the esophagus by colon or jejunum was preferred. In the case of chronic esophageal strictures, either posterior mediastinal replacement of the esophagus or substernal bypass was performed. The esophageal substitute must be encased in a plastic bag so that when it is pulled up, the bag will prevent disruption of the vessels. In the case of complete obstruction of the esophageal orifice, a Baker's dilator was used from the hypopharynx to direct and cut an orifice in the cervical wound. After careful evaluation of the proximal esophagus and hypopharynx, the anastomosis in the neck was performed above the level of the abnormal esophageal mucosa. When the hypopharynx was opened wide, a hypopharyngoileostomy or hypopharyngocolostomy was performed. When an esophagocolostomy was required, it was done with one-layer or two-layer interrupted sutures. Partial resection of the manubrium and clavicular head was required for patients with a narrow thoracic outlet. Patency of the whole alimentary tract should be checked before closure of the incisional wound. Closure of the linea alba and peritoneum must be done with the utmost care to avoid interference with the passage of the esophageal substitute from the substernum into the peritoneal cavity. Retention sutures were usually placed in the abdominal wound to prevent wound disruption. The associated gastric strictures were surgically corrected by any one of the following methods: esophagogastrectomy, antrectomy, side-to-side cologastrostomy, or anchorage of the anastomosis to the narrowing segment of the peripyloric region (Fig 1).

Table 2. Reconstruction of Esophagus in 75 Patients[a]

Operation	No. of Patients
Emergency esophagogastrectomy in acute stage + elective reconstruction of esophagus	9 (12)
Emergency esophagogastroduodenectomy and partial jejunectomy in acute stage + elective reconstruction of esophagus	1 (1.3)
Elective esophagectomy + replacement of esophagus	4 (5.3)[b]
Elective reconstruction of esophagus (bypass)	61 (81.3)

[a] Numbers in parentheses are percentages. [b] Replacement was accomplished through posterior mediastinum.

Perioperative Care

Feeding through a jejunostomy was necessary for nutrition in patients undergoing total esophagogastrectomy. Hyperalimentation was used for severely malnourished and very ill patients. Oral hygiene should be practiced,

Table 3. Esophageal Substitutes for Reconstruction in 75 Patients[a]

Substitute	No. of Patients
Long segment of ileum + ascending colon	42 (56)
Short segment of ileum + ascending colon	18 (24)
Ascending and transverse colon	3 (4)
Ascending, transverse, and left colon	1 (1.3)
Transverse and left colon	6 (8)
Jejunum	2 (2.7)
Stomach	3 (4)

[a] Numbers in parentheses are percentages.

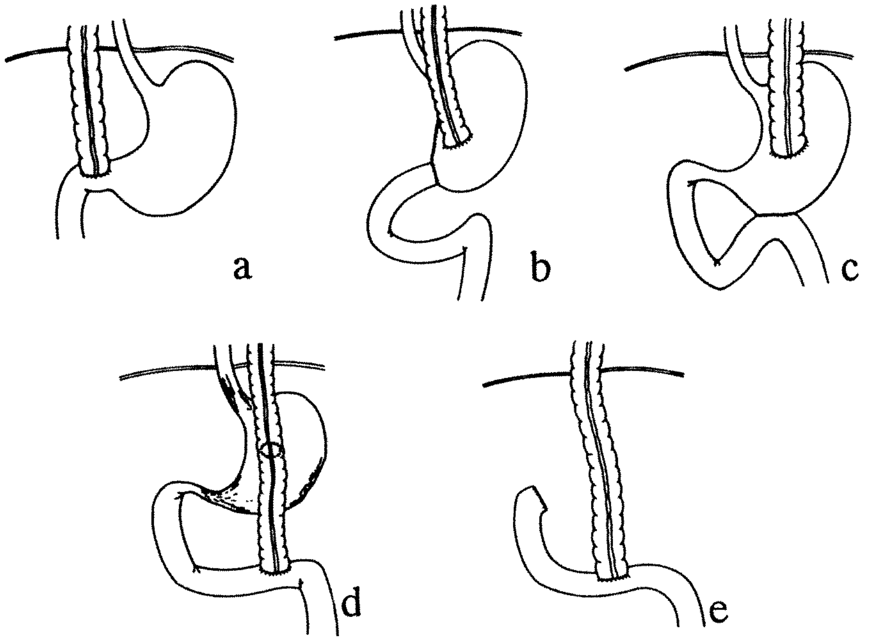

Fig 1. Abdominal procedures for associated gastric strictures: (a) cologastroduodenostomy; (b) gastroduodenostomy and cologastrostomy; (c) gastrojejunostomy and cologastrostomy; (d) cologastrostomy and colojejunostomy; and (e) gastrectomy and colojejunostomy.

and the airway should be carefully checked before operation. The psychological condition and the physical condition of the patient should be stabilized before operation.

Immediately after operation, a chest roentgenogram was made to check for pneumothorax. The presence of pneumothorax necessitated tube thoracostomy.

After an adequate bowel movement, the patient was fed nasogastrically for 2 weeks. Then oral feeding was allowed provided there was no leakage from the anastomosis. Swallowing was difficult when the anastomosis was done above the cricopharyngus. Patients were instructed to train themselves by swallowing small amounts until swallow function was regained.

Follow-up

Two weeks after reconstruction of the esophagus, barium meal studies were routinely carried out to evaluate the patency of the conduit and the condition of the anastomoses. After discharge from the hospital, patients were monitored in the outpatient clinic. The ability to swallow, body weight, and activity were recorded. The length of follow-up ranged from 2 months to 15 years and usually was at least 6 months. Data for the follow-up study were obtained through clinic visits and questionnaires. In some cases, complications developing immediately after operation or during long-term follow-up were considered operative morbidity. Deaths within 1 month after operation were defined as operative deaths.

Swallowing Time Measurement

Under fluoroscopy, the swallowing time of barium from the pharynx to the level of the diaphragm was measured. To evaluate the conduits, the swallowing time of 6 randomly chosen patients who had right ileocolon transplantation was compared with that of 6 patients who had transverse and left colon transplantation. Six patients with a duodenal ulcer were used as the control group.

Results

Results were graded as "good," "fair," and "poor." Results were categorized as "good" when the patient was symptom-free, capable of swallowing a regular diet, and gaining weight accordingly; "fair" when the patient could swallow but with regurgitation and had a decrease in daily activities; and "poor" when the patient had dysphagia, regurgitation, and aspiration. Close to 90% (n = 67) of the patients had good results. Four patients (5.3%) had fair results, including 2 patients in whom there was redundant right ileocolon and 2 patients in whom the entire stomach had been pulled up. Four of 15 patients with pharyngoileostomy had poor results, including 1 with an associated tracheolaryngeal stenosis and another with laryngeal stenosis.

There were no deaths in this series. Complications of esophageal reconstruction included leakage from the anastomosis, redundancy of the esophageal substitute, intestinal obstruction, obstruction of the esophageal substitute, pneumothorax, internal herniation, chronic anemia caused by the formation of a gastric mucocele, stenosis of the anastomosis, wound dehiscence, and obstruction of the gastrojejunostomy caused by progressive contraction of the antrum (Table 4). In 5 patients (6.7%), all with an ileocolon transplant, the cervical anastomosis leaked. In 3 patients, anastomotic stenosis was corrected by revision. The pneumothoraces were treated by tube thoracostomy. Obstruction of the intestine, obstruction of the esophageal substitute, and internal herniation were surgically corrected through a laparotomy. In 1 patient with severe gastric stricture, colojejunostomy was done instead of cologastrostomy. This led to the development of a gastric mucocele complicated by chronic anemia and was resolved with a side-to-side cologastrostomy.

The swallowing time was 2 to 4 seconds in the transverse and left colon transplant group compared with 5 to

Table 4. Complications After 75 Esophageal Reconstructions[a,b]

Complication	No. of Patients
Early	
Cervical anastomotic leakage	5 (6.7)
Pneumothorax, unilateral or bilateral	7 (9.3)
Abdominal anastomotic leakage	1 (1.3)
Wound dehiscence	1 (1.3)
Late	
Intestinal obstruction	5 (6.7)
Stenosis of cervical anastomosis	3 (4)
Redundant esophageal substitute	2 (2.7)
Gastric mucocele with chronic anemia	1 (1.3)
Obstruction of esophageal substitute	1 (1.3)
Internal herniation	1 (1.3)
Obstruction of gastrojejunostomy caused by progressive antral stricture	1 (1.3)

[a] Some of the 24 patients had more than one complication. [b] Numbers in parentheses are percentages.

9 seconds in the right ileocolon transplant group. It was within 2 seconds in the control group.

Comment

After resection for ingestion of a corrosive agent, the substernal route was favored for colon bypass. The posterior mediastinal route was not considered because of severe fibrosis. Patients with chronic severe esophageal strictures required bypass of the entire esophagus or replacement of the resected esophagus. In the bypass procedure, the thoracic esophagus was left in continuity with the stomach. The occurrence of mucocele and of cancer after corrosive stricture of the esophagus is rare [1, 3]. To decrease the risk of postoperative bleeding and to save time, esophagectomy was not routinely done. However, when there was a severe gastric stricture or esophagorespiratory fistula, esophagectomy was indicated. Preference was given to the posterior mediastinal route because it was the shortest [1] and provided a good passageway. The esophageal stricture frequently occurred at the level of the hypopharynx, sternal notch, and supraaortic region and less often at the supradiaphragmatic level. The proximal esophagus was deeply dissected, and the distal stump was closed at the subclavicular level, even in the case of a hypopharygeal anastomosis. This could explain why no mucocele of the esophagus was found in this series. However, a gastric mucocele developed 2 years after an ileocolon bypass to the jejunum in 1 patient whose esophagus sloughed out 9 days after corrosive injury. Hence, esophagectomy was performed only if there was a severe gastric stricture or esophagorespiratory fistula. Gastrectomy was usually done for a severe gastric stricture. In the preoperative evaluation, 1 patient with an esophageal stricture of 12 years' duration was found to have inoperable carcinoma and was excluded from this series.

The criteria used in choosing the esophageal substitute were adequate blood supply, minimal amount of surrounding fatty tissue, no redundancy, and isoperistalsis. The transverse or left colon was a favorable substitute because of its suitable size and vessels [4–7]. The right ileocolon was a good substitute because of the ability of the ileocecal valve to prevent regurgitation. When the substitute comprised a long segment of the ileum and the right colon, the cecum was usually located at the lower part of the retrosternum, and this contributed to the patency of the substitute. In contrast, use of a short segment of the ileum and the right colon occasionally caused compression of the cecum by the narrow thoracic outlet, thereby creating a difficult passage. In most cases, the stomach was not a suitable candidate for esophageal substitution because it was moderately or severely injured by acid. The reconstruction of a high-level stricture required more than 30 cm of the ileum and the right colon. A jejunum with friable mesentery and incompatible vessel length was considered last as an esophageal substitute in the acid-injured patients whose colon was not available.

Acid agents cause more damage to the stomach than to the esophagus. In contrast, an alkaline substance frequently causes esophageal burns and stricture and only occasionally produces gastric injury. The damaged areas of the stomach are related to the patient's posture while swallowing and to the type and the amount of the agent ingested. Among acid-injured patients, the fundus is the primary site of perforation in the acute stage. In the case of associated severe gastric stricture, combined resection of the esophagus and the stomach was carried out. In the case of moderate gastric stricture, surgical correction by antrectomy, side-to-side cologastrostomy, esophagogastrectomy, or anchoring of the anastomosis to the narrowing segment of the peripyloric region was performed.

Esophageal stricture associated with esophagorespiratory fistula is a unique problem. In patients with caustic esophageal stricture and symptoms of severe cough, the presence of an esophagorespiratory fistula should be suspected. Bronchoscopy and esophagography are useful diagnostic modalities. In 1978, Burrington and Raffensperger [8] reported the successful treatment of 4 children by end-cervical esophagostomy with closure of the distal stump of the cervical esophagus, gastrostomy, and complete disconnection of the intraabdominal esophagus from the stomach. An attempt to close the tracheobronchial defect through a right or left thoracotomy should be accompanied by esophagectomy and reconstruction of the esophagus. We operated on a patient with an associated tracheoesophageal fistula and stenosis of the intermediate bronchus. The patient required sleeve resection of the intermediate bronchus and repair of the tracheal defect in addition to thoracic esophagectomy. Substernal right ileocolon bypass was performed. Another patient with an associated esophagobronchial fistula required closure of the left bronchial defect through a left thoracotomy. Esophageal replacement by transverse and left colon through the posterior mediastinum was done.

We experienced a technical difficulty with dissection of the esophagus and repair of the tracheobronchial defect because of severe fibrosis.

A high level of esophageal stricture was occasionally obscured in the esophagogram. Hence, in the exploration of the neck, the proximal cervical esophagus was routinely checked by operative endoscopy or the stricture detected by resistance to the passage of Baker's dilators. In the presence of hypopharyngeal stricture, results of reconstruction were unsatisfactory. Tran Ba Huy and Celerier [2] in 1988 reported that return of deglutition assuring normal nutrition was obtained in 11 of 18 patients with hypopharyngeal stenosis. In our series, 4 of 15 patients with pharyngeal anastomoses showed poor results. In this type of stricture, the cervical dissection was made upward to the left inferior constrictor and cricopharyngeal muscles. Anastomosis to the piriform sinus or pharynx was relatively difficult.

Most complications occurred early in our experience. Their incidence has been minimized through an increase in experience, improved technical planning, and careful preservation of the vascular competence of the transplant. Pneumothorax occurred when the substernal tunnel was created by the surgeon's hand. It was prevented by careful dissection with a flexible board. Intestinal obstruction was occasionally found, but internal herniation or obstruction of the esophageal substitute was rare. Leakage was usually related to tension anastomosis, inadequate blood supply, or food retention caused by redundancy of the ileocolon. Leakage from the cervical anastomosis usually stopped spontaneously. Anastomotic stenosis after leakage was corrected by dilation or revision. These complications did not occur in patients with a transverse and left colon transplant.

The thoracic outlet should be opened widely by blunt and sharp dissection to create a space large enough for the passage of the esophageal substitute and its subsequent food contents. An additional jejunostomy is not routinely done in an esophageal reconstruction except in the case of a difficult pharyngoileostomy.

In the postoperative barium swallow study, we found that patients with a transverse and left colon transplant had a shorter swallowing time than those with a right ileocolon transplant. In addition, the transverse and left colon had parallel vessels to facilitate mobilization and dissection. There were no complications in the 6 patients with transverse and left colon transplants.

In conclusion, because of damage to the stomach in most of our acid-injured patients, the right ileocolon was used as the esophageal substitute in most instances. However, although our experience comprises just 6 patients, the transverse and left colon could be the best choice for esophageal replacement because of ease of technique, good food passage, and absence of complications.

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Late Complications of Plombage

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Plombage was used commonly in the management of tuberculosis before the early 1950s. From 1977 through 1990, 4 patients were seen with complications of plombage performed decades previously. Lucite spheres were used in 3 patients and paraffin in 1. One patient had bilateral apical plombage. In all cases, complications were related to infection or migration of the foreign material. Two patients had extrusion of foreign material or fluid into the chest wall. One patient had hemoptysis and infection due to erosion of a Lucite sphere into the lung. Another had intestinal obstruction subsequent to erosion into the esophagus. The patient with bilateral plombage had development of asynchronous complications on both sides. Treatment consisted of removal of the foreign material and individualized management of the remaining space. There were no operative deaths and the outcome was good in all cases.

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An important chapter in the history of thoracic surgery involves the treatment of tuberculosis. A variety of operations were employed for management of tuberculosis and its complications.

Plombage was used commonly in the early and mid-twentieth century [1–6]. Today, successful pharmacologic therapy has supplanted surgical treatment of tuberculosis, and operation is reserved for complications of the disease [7–10]. However, there still remains a group of patients who had plombage performed 40 or more years ago. These patients may be seen with late complications of earlier operations. The purpose of this article is to present our experience in the management of various complications of plombage performed in the distant past.

Material and Methods

We identified all patients seen from 1977 through 1990 with complications of previous plombage. Medical records were reviewed and information was obtained regarding the original plombage procedure, subsequent complications, and the management of these complications. Late follow-up was obtained by telephone for all living patients in July 1991.

Results

Four patients with complications of previous plombage procedures were identified (Table 1). The plombage operations were performed from 1946 through 1952, at which time the mean patient age was 27 years. Lucite spheres were used in 3 patients and paraffin in the other. One patient underwent bilateral plombage procedures.

The mean interval from plombage to occurrence of complications was 37 years. The mean age when complications were recognized was 64 years. Complications were related to infection or migration of the foreign material. The patient with bilateral plombage had development of nonsimultaneous complications on each side.

Management consisted of removal of foreign material in all patients. In 1 patient, a Lucite sphere that had migrated out of the thorax could not be located intraoperatively. The cavity was managed by open drainage in three instances. In 1 patient, the empty pleural space was filled with antibiotic solution. Thoracoplasty was used to obliterate the apex in 1 patient. The presentation and management of plombage-associated complications were quite different, as detailed below.

Patient 1

Patient 1 underwent bilateral sequential apical plombage for tuberculosis in 1946. In 1977, he had evidence of infection in the left apex (Fig 1). Multiple Lucite spheres were removed, and the remaining space was drained by limited rib resection. Convalescence was uncomplicated and the cavity gradually closed without further intervention.

Approximately 18 months later he was readmitted for intestinal obstruction. A Lucite ball was removed from the jejunum at laparotomy. Retrospective review of an intravenous pyelogram performed several weeks earlier showed a Lucite sphere in the abdomen (Fig 2). An esophagogram demonstrated that the sphere had entered the gastrointestinal tract by fistulization into the thoracic esophagus (Fig 3). Thoracotomy was performed and all foreign material was removed. The defect in the esophagus was closed with a muscle flap and thoracoplasty was performed to obliterate remaining space. A postoperative esophageal leak was successfully managed with drainage and parenteral nutritional support. The patient recovered without further complications. Hemoptysis from chronic

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Table 1. Complications of Plombage

Patient No.	Sex	Side	Material Used	Year of Plombage	Age at Plombage (y)	Age at Complication (y)	Interval from Plombage to Complication (y)
1	M	Bilateral	Lucite spheres	1946	23	54/55	31/32
2	F	Left	Paraffin	1952	42	77	35
3	M	Left	Lucite spheres	1948	26	67	41
4	M	Left	Lucite spheres	1949	15	56	41

bronchiectasis later developed and necessitated repeated bronchial artery embolization. He died 12 years after the last operation.

Patient 2

Patient 2 underwent left apical plombage with paraffin and resection of two ribs at age 42 years. Thirty-three years later, an axillary "cyst" was excised by an outside general surgeon. The patient was ultimately referred to this institution for a persistent draining fistula from the axilla. Evaluation demonstrated communication with the apex of the left hemithorax. Treatment consisted of removal of all the paraffin; densely calcified tissue in the base of the wound was not excised. A modified Eloesser flap was performed and the cavity was managed by open drainage. The patient recovered uneventfully and is doing well 4 years later. She does not desire closure of a small remaining wound.

Patient 3

Patient 3 underwent left pneumonectomy for complicated tuberculosis in 1948. Two weeks later the hemithorax was filled with Lucite spheres, presumably to prevent mediastinal shift and hyperinflation of the contralateral lung (Fig 4). More than 40 years later, when the patient was 67 years old, a large mass developed in the left anterolateral chest wall. Radiologic evaluation indicated that the mass represented fluid that had been extruded out of the chest (Fig 5). At operation, 36 spheres and a large amount of

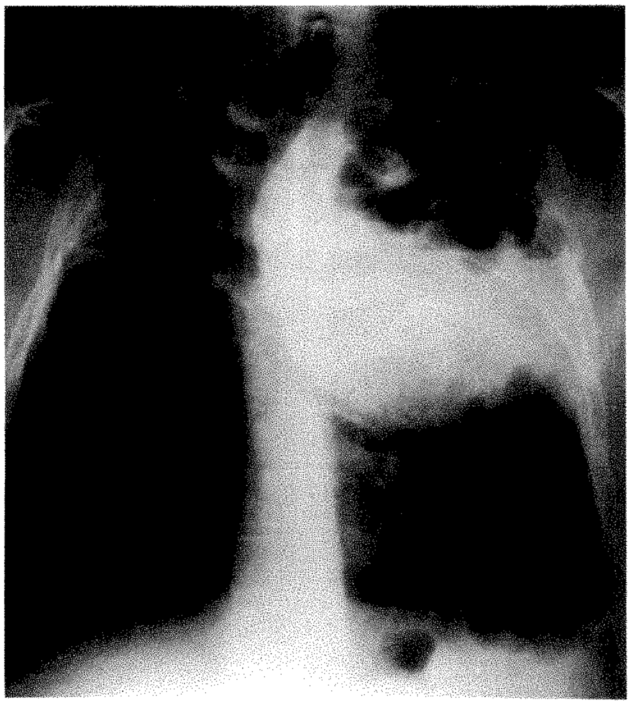

Fig 1. (Patient 1.) Radiograph of the chest shows bilateral apical Lucite spheres. Infection on the left side is indicated by fluid in and around the spheres.

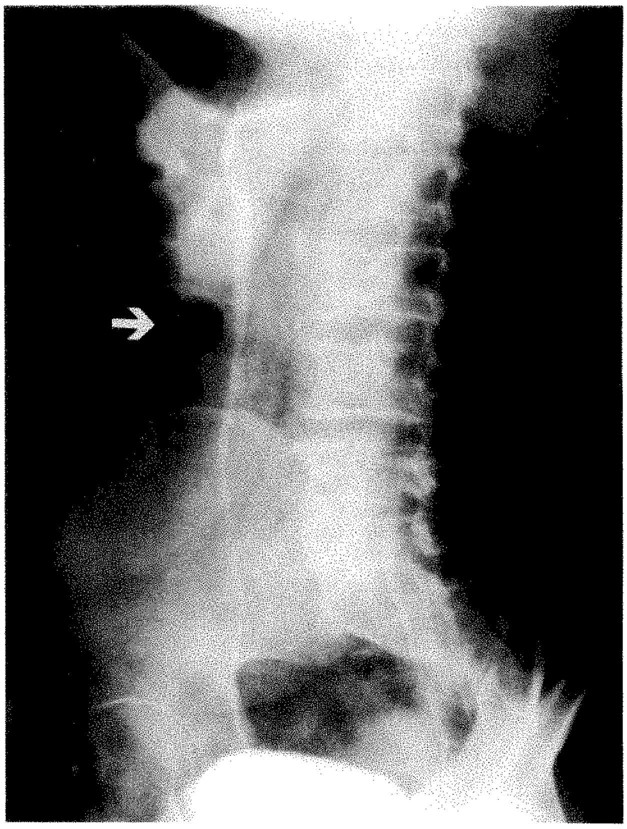

Fig 2. (Patient 1.) Radiograph of the abdomen (intravenous pyelogram) shows a Lucite sphere in the gastrointestinal tract (arrow).

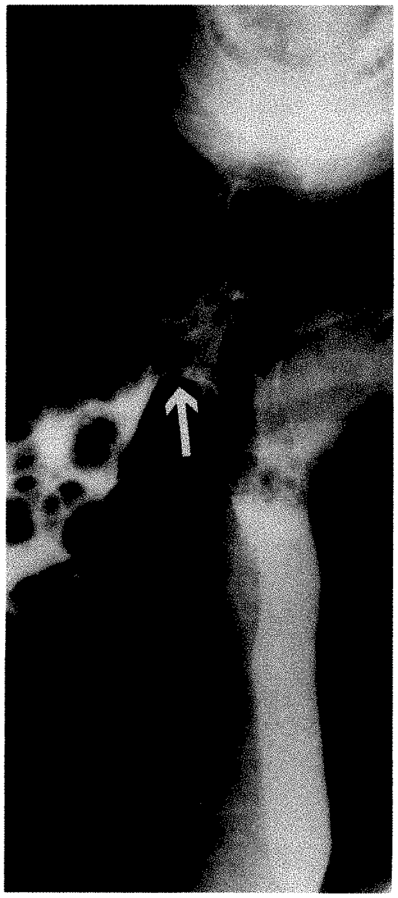

Fig 3. (Patient 1.) Lucite spheres in the right apex are outlined by orally administered barium. The site of communication with the esophagus is demonstrated (arrow).

turbid yellow fluid were removed. An irrigation system was placed and the wound was closed primarily. Operative cultures were initially sterile; consequently, the chest

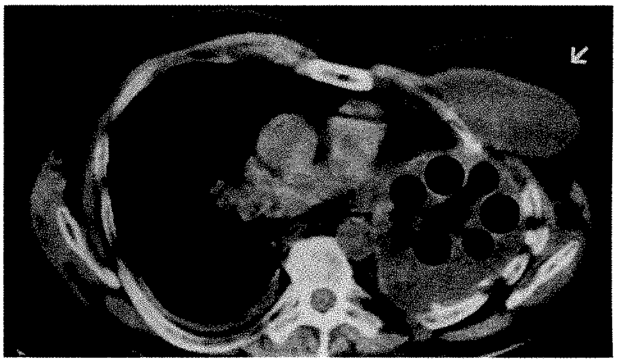

Fig 5. (Patient 3.) Computed tomographic scan shows a large soft tissue mass (arrow) *due to extrusion of fluid from chest. Several Lucite spheres are seen within the thorax.*

was filled with antibiotic (cephalosporin) solution and the drainage system was removed. Subsequently, *Mycobacterium tuberculosis* was identified in cultures of the intrathoracic fluid. Antituberculous therapy was instituted. The patient is doing well 15 months postoperatively.

Patient 4

Patient 4 underwent left upper lobectomy, Lucite sphere plombage, and thoracoplasty in 1949 for tuberculosis. Forty-one years later, he had fever and hemoptysis. Bronchoscopy demonstrated the source of bleeding to be the residual left lung. Because of poor general condition and compromised respiratory function, initial management consisted of antibiotics and pulmonary toilet. When the medical regimen failed, he was referred for surgical therapy. Twenty-one Lucite spheres were removed, several of which contained murky fluid (Fig 6). One ball had migrated well out of the thorax and could not be located. The cavity and bronchopleural fistula were managed by packing. The patient is doing very well 13 months post-

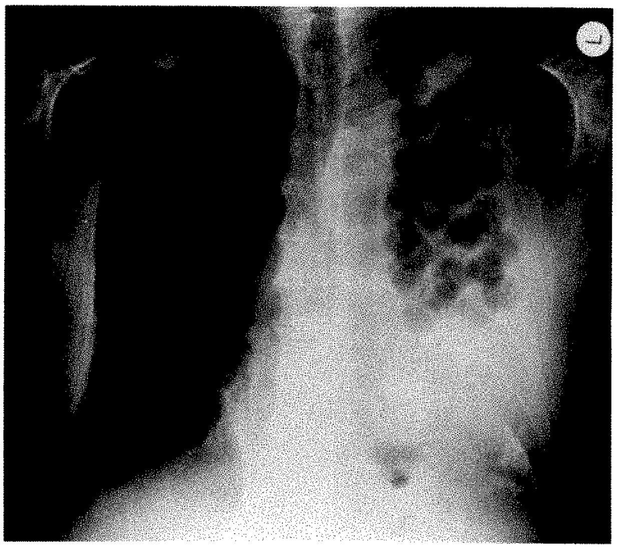

Fig 4. (Patient 3.) Radiograph shows 36 Lucite spheres that were inserted in the chest after left pneumonectomy. The mediastinum is midline.

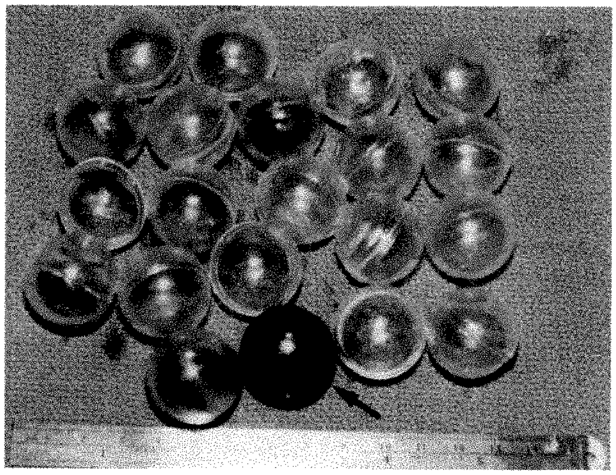

Fig 6. (Patient 4.) Twenty-one Lucite spheres that were removed 41 years subsequent to initial plombage operation. One ball is filled with murky fluid (arrow)*; several others contain lesser quantities of fluid. Each sphere is approximately 2.5 cm in diameter.*

operatively. Although a small air leak persists, the wound is free of infection; definitive closure is planned for the near future.

Comment

More than 2,400 years ago, Hippocrates inserted a pig's bladder into a patient's chest and inflated it [1]. Although the rationale for this procedure is unknown, it likely represents the first use of plombage. Collapse therapy for tuberculosis was initially performed by Tuffier in 1891 [1]. Over the next half century, various forms of collapse therapy including thoracoplasty and plombage were used extensively for the management of tuberculosis.

At least 29 different materials were used to maintain collapse of affected areas of lung [1]. Tuffier used omentum and fresh lipoma for this purpose. In 1913, gas was used by Tuffier, and also by Mayer, to maintain the extrapleural space after pneumonolysis. In the same year, Baer introduced paraffin mixtures for this purpose. In 1920, Archibald [5] reported the use of viable pedicled muscle to fill the extrapleural apical space. Other materials used for plombage include gauze sponge, silk, wax, various oils, gelatin, rubber balloons, drawing crayons, and lead bullets [1]. In 1946, Wilson [2] reported his experience using balls made from methyl methacrylate (Lucite) for plombage. This material appeared to have advantages in that it was relatively nonirritating, lightweight, and radiolucent [2, 4]. In 1948, Johnson and co-workers [6] used Lucite spheres to fill the chest after pneumonectomy to prevent overinflation of the remaining lung.

The ideal plombage material would produce reliable and permanent collapse, would not migrate, and would resist infection. However, all of the materials used had important shortcomings. Paraffin was prone to infection and extrusion [1, 5]. Despite the theoretical advantages of Lucite, problems became apparent with early clinical experience [1, 3]. Migration and erosion of the Lucite spheres were particularly troublesome. In 1949, Walkup and Murphy [1] concluded that the optimum filling material for maintenance of extrapleural space had not been found.

The search for the ideal plombage material was soon ended. The introduction of streptomycin in 1945, paraaminosalicylic acid in 1946, and isoniazid in 1951 dramatically changed the therapy of tuberculosis [7]. Today, pharmacological treatment of tuberculosis is effective, and only rarely is surgical intervention indicated. Complications for which operation may be necessary include drug-resistant disease, bronchiectasis, and hemoptysis [8, 9]. Surgical therapy generally involves resection of infected or destroyed lung tissue [8, 9]. The present role of collapse therapy is quite limited. Thoracoplasty is still used occasionally for complicated tuberculous empyema [10]. The last report on plombage therapy (1973) describes use of a silicone mammary prosthesis in a patient with hemoptysis due to tuberculosis [11]. Several recent articles discuss complications of plombage performed many years earlier [12–14].

Plombage is rarely performed by contemporary thoracic surgeons. This procedure may soon be of historical interest only. However, there exists a group of patients who underwent plombage procedures in the distant past. Some of these patients will return with complications requiring treatment by thoracic surgeons.

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Magnetic Resonance Imaging of the Brain Before and After Open Heart Operations

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Magnetic resonance imaging of the brain was performed in 29 adult male patients before and 1 week after elective coronary artery bypass grafting to study the cerebral effect of cardiopulmonary bypass. The mean age of the patients was 60 years (range, 45 to 69 years). During cardiopulmonary bypass, either a bubble oxygenator without an arterial line filter (n = 9), a bubble oxygenator with a depth adsorption filter (n = 10), or a flat-sheet membrane oxygenator without a filter (n = 10) was used. The mean bypass time was 88 minutes (standard deviation, 31 minutes) and did not differ significantly between the three groups. Preoperative magnetic resonance imaging revealed high signal intensity foci on T2-weighted images (white matter abnormalities) in 17 (59%; 95% confidence limits, 39% to 76%) of the 29 patients, all of which were nonspecific and of the common type considered to be related to aging, and all were unchanged at the postoperative examination. Preoperative and postoperative frontal horn indices, bicaudate diameters, and third ventricle widths did not differ significantly regardless of oxygenator type or whether or not an arterial line filter was used during cardiopulmonary bypass. Two patients (7%; 95% confidence limits, 1% to 23%), both receiving bubble oxygenation (1 without a filter and 1 with an arterial line filter) sustained a cerebral infarction during cardiopulmonary bypass.

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Cerebral pathology related to cardiopulmonary bypass (CPB) is generally caused by intraoperative embolization or by cerebral hypoperfusion during or after operation [1–7]. Embolic complications have become much less frequent with the advent of modern surgical techniques and novel CPB equipment, particularly membrane oxygenation [4, 6, 8]. The cerebral blood flow during CPB is mainly regulated by arterial carbon dioxide tension, cerebral oxygen consumption, depth of anesthesia, and body temperature [9, 10].

Magnetic resonance imaging (MRI) of the brain is claimed to be a sensitive tool for evaluating cerebral injury after open heart operations [11], providing high-quality images with superior depiction of cerebral anatomy [12–14]. Despite this fact, MRI has not been used as frequently as computed tomography to investigate the incidence of cerebral complications after CPB, probably partly because of the relative scarcity of MR units as compared with computed tomographic facilities to date. However, both MRI and computed tomography of the brain have demonstrated dilatation of ventricles, a finding indicating cerebral atrophy, in children after open heart procedures [1, 2]. To our knowledge, no similar study has been reported in adults.

The twofold purpose of this study was to assess the overall rate of brain complications in patients examined with MRI before and after coronary artery bypass grafting and to investigate whether these complications occurred regardless of oxygenator type or whether or not an arterial line filter was used during CPB.

Material and Methods

Male patients less than 70 years of age undergoing elective isolated coronary artery bypass grafting were studied. Patients with a history of cerebrovascular, neurological, carotid artery, or coagulation disorders or alcoholism were excluded from the study. Eighteen patients (62%) had a previous history of acute myocardial infarction, 10 (35%) had hypertension, 9 (31%) had hyperlipidemia, and 3 (10%) had diabetes mellitus. Chest roentgenograms did not show calcifications of the ascending aorta. Four patients (14%) had left main stem stenosis. Angiography demonstrated stenosis of at least three major coronary artery branches.

The informed consent of each patient was obtained, and the study was approved by the local committee on ethics of Karolinska Hospital.

Thirty patients operated on between June 1987 and March 1989 and fulfilling the inclusion criteria were randomized prospectively to one of three different methods of CPB: a bubble oxygenator without a filter (group 1, n = 10), a bubble oxygenator with a filter (group 2, n = 10), or a membrane oxygenator without a filter (group 3, n = 10). One patient assigned to group 1 did not consent to a postoperative examination and was excluded from the study.

Perioperative Management

Anesthesia was induced with fentanyl citrate (4 to 7 μg/kg), midazolam hydrochloride (0.15 to 0.50 mg/kg),

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and pancuronium bromide (0.1 mg/kg) and was maintained with fentanyl (0.3 mg/h), midazolam (3 mg/kg), oxygen, and nitrous oxide. Acid-base management was maintained at a non–temperature-corrected arterial carbon dioxide tension of approximately 40 mm Hg (5.3 kPa) and at a pH of 7.40 (alpha-stat principles).

A bubble oxygenator (Shiley S-100; Shiley Inc, Irvine, CA) with an incorporated three-stage filter comprising a polyurethane sponge with 20 and 80 pores per square inch and a 105-μm polyester screen was used in 20 of the operations. The Shiley cardiotomy reservoir (Card F Plus) had an integral filtration system with a nonmigrating polyester depth medium and a 20-μm nylon screen filter. A reticulated polyurethane sponge was used for defoaming. In ten of these 20 operations, a depth adsorption filter (Swank High Flow 6000; Pioneer Filter Inc, Beaverton, OR) was connected to the arterial line. The pressure difference across the filter was monitored, and a bypass line was installed as a safeguard. In ten operations, a flat-sheet membrane oxygenator (Shiley M-2000) was used without an arterial line filter. Identical polyvinyl chloride tubing, roller pump, heat exchanger, and heart-lung machine (Sarns 7000) were used in all operations. Two liters of crystalloid priming volume was used. Heparin sodium anticoagulation, before and during CPB, as well as neutralization with protamine sulfate after CPB, was monitored by means of the activated clotting time (Hemochron 400 ACT). The activated clotting time value was prolonged to at least 480 seconds during bypass.

Cardiopulmonary bypass was carried out with nonpulsatile flow, moderate core cooling (28°C), and hemodilution (hematocrit of 0.25 to 0.30). Cold multidose potassium cardioplegia was used for myocardial protection (St. Thomas' solution at 4°C). Pump flow during hypothermia (28°C) was kept at 1.6 to 1.8 $L \cdot min^{-1} \cdot m^{-2}$ to maintain a mean arterial blood pressure of approximately 50 mm Hg.

Magnetic resonance imaging of the brain was performed on a 0.5-T unit (Magnetom; Siemens) before the operation and was repeated 1 week after the operation. After an initial sagittal scout, the entire brain was scanned with a standard spin-echo sequence with a repetition time of 2,300 ms and two echos with a 35- and 120-ms delay. This protocol provides a set of proton density weighted images with good anatomical detail (echo time of 35 ms) and another set of T2-weighted images (echo time of 120 ms) with high sensitivity to most types of brain pathology including ischemic lesions. The slice thickness was 8 mm with a 2-mm gap between slices. The duration of each examination was approximately 30 minutes.

Analysis of the MR images obtained on both occasions included a thorough mapping of all signal changes, calculation of a frontal horn index (ie, the greatest distance between the lateral walls of the frontal horns divided by the greatest inner-skull diameter), measurement of the bicaudate diameter (the shortest distance between the medial walls of the head of the caudate nuclei), and measurement of the transverse diameter of the midportion of the third ventricle (Fig 1). A frontal horn index of greater than 0.33 and a third ventricle width of greater

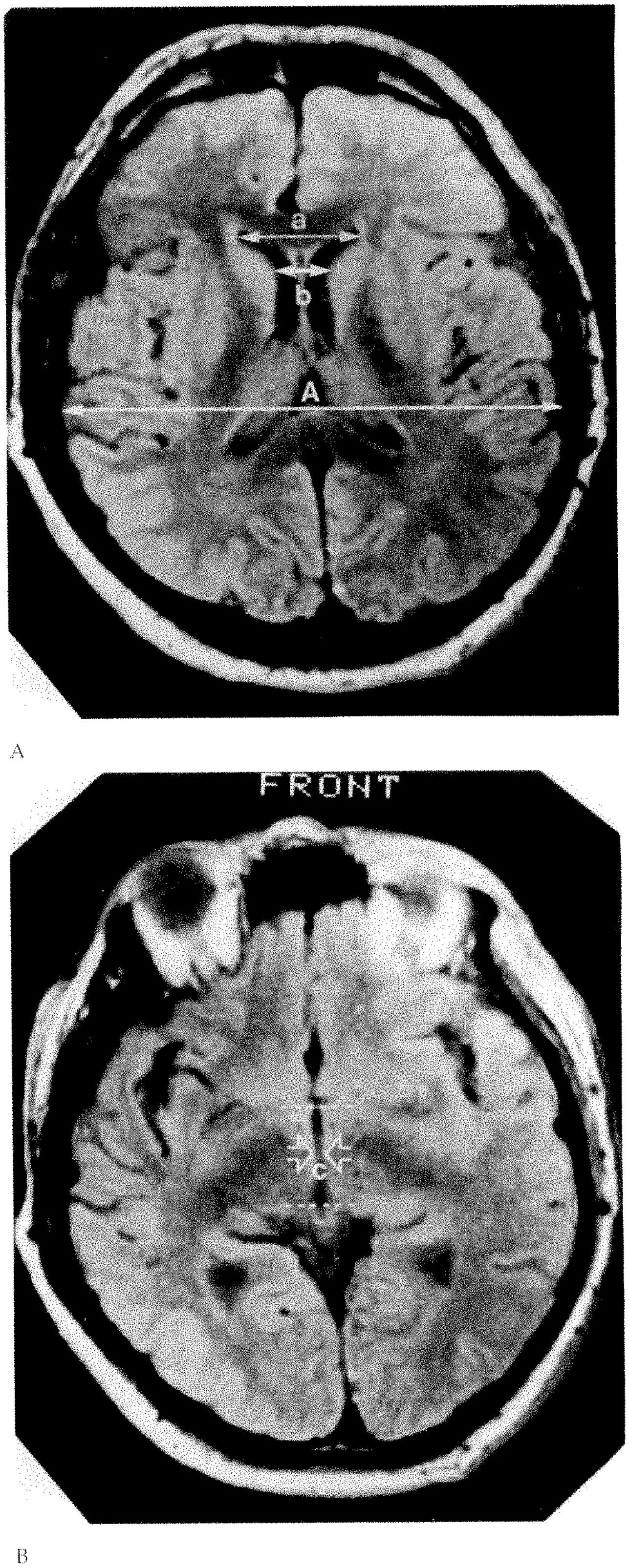

Fig 1. Magnetic resonance images of the brain. (A) Arrows *indicate the frontal horn index, ie, the greatest distance between the lateral walls of the frontal horns* (a) *divided by the greatest inner-skull diameter* (A), *and the bicaudate diameter, ie, the shortest distance between the medial walls of the head of the caudate nuclei* (b). *(B)* Arrows *indicate the transverse width of the midportion of the third ventricle* (c).

Table 1. Patient Characteristics in Relation to Type of Oxygenator and Use of Arterial Line Filter

	Bubble Oxygenator		Membrane Oxygenator	
Variable	No Filter (n = 9)	Filter (n = 10)	No Filter (n = 10)	p Value
Age (y)	58 (6)	61 (6)	60 (6)	<0.70
Average no. of grafts per patient	4.1	4.3	3.5	<0.50
Perfusion time (min)	96 (29)	93 (40)	74 (16)	<0.20
Aortic occlusion time (min)	46 (20)	50 (32)	36 (11)	<0.50

[a] Data are shown as the mean with the standard deviation in parentheses.

than 8 mm was classified as pathological [15]. All images were evaluated by the same neuroradiologist.

Statistical Methods

Continuous variables are described as means with one standard deviation, 95% confidence limits (95% CL), or range. Student's paired t test or the Mann-Whitney U test was employed to compare two samples. The Kruskal-Wallis one-way nonparametric analysis of variance was used to compare three samples. Discrete variables were analyzed by Fisher's exact test. The null hypothesis was rejected if the p value was less than 0.05.

Results

Clinical Course

The mean age of the 29 patients was 60 years (range, 45 to 69 years), and they received an average of 4.2 grafts. The mean CPB time was 88 minutes (standard deviation, 31 minutes), and the mean aortic occlusion time was 44 minutes (standard deviation, 23 minutes). Clinical variables did not differ significantly between the three groups (Table 1). There were no early deaths and no reoperations for early postoperative bleeding. One patient in group 2 sustained a minor perioperative myocardial infarction but had an uneventful clinical course.

Preoperative MRI

High signal intensity foci on T2-weighted images were observed in the white matter in 17 (59%; 95% CL, 39% to 76%) of the 29 patients. These changes were all nonspecific and of the common type considered to be related to aging. One patient had two arterial aneurysms (anterior communicating artery and right middle cerebral artery), 1 had a left-sided temporal hygroma, probably traumatic in origin, and a few had marked cortical atrophy. No other pathological condition was recorded in the preoperative scan. Measurements of the frontal horn index and transverse width of the third ventricle were within the normal range in all patients (Figs 2, 3).

Postoperative MRI

The high signal intensity foci on the T2-weighted images observed in the preoperative scans were all unchanged at the postoperative examinations. In 2 patients (7%; 95% CL, 1% to 23%), MRI demonstrated an infarction that was not seen before the operation. One patient in group 1 had an infarction measuring 3 × 2 × 3 cm localized in the left occipital lobe (Fig 4). In the other patient, who was in group 2, a 0.5 × 0.5 × 0.5-cm infarction was found in the

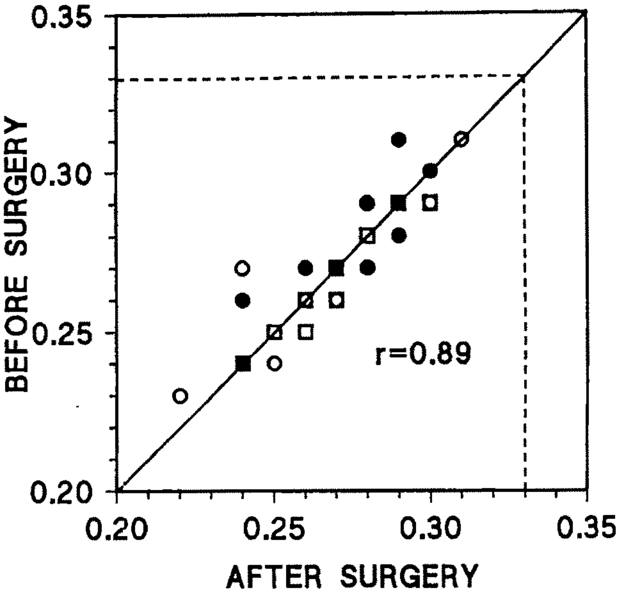

Fig 2. Frontal horn index in 29 patients before and after operation. The broken line *indicates the upper range in healthy controls. The coefficient of correlation (r) is calculated. (○ = bubble oxygenator without filter; ● = bubble oxygenator with filter; □ = membrane oxygenator without filter.)*

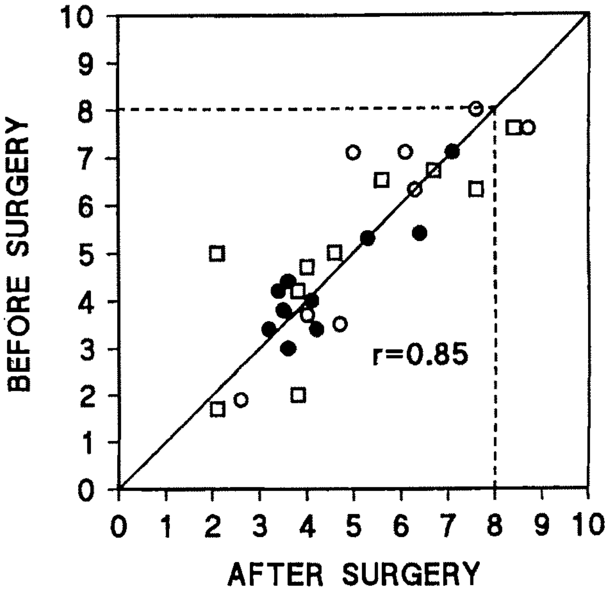

Fig 3. Diameter of the third ventricle (in millimeters) in 29 patients before and after operation. The broken line *indicates the upper range in healthy controls. The coefficient of correlation (r) is calculated. (○ = bubble oxygenator without filter; ● = bubble oxygenator with filter; □ = membrane oxygenator without filter.)*

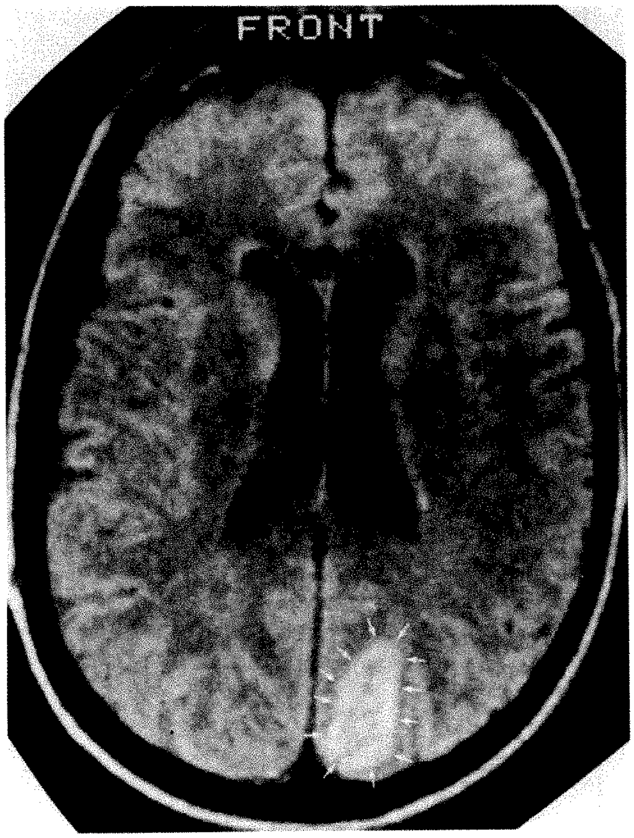

Fig 4. Magnetic resonance imaging of the brain after coronary artery bypass grafting in a patient randomized to a bubble oxygenator without an arterial line filter. The arrows *indicate a postoperative cerebral infarction in the left occipital lobe.*

posterior part of the frontal lobe. These 2 patients did not have clinical signs of neurological dysfunction during their postoperative courses. There were no significant differences between preoperative and postoperative frontal horn indices, bicaudate distances, or third ventricle transverse diameters in the three groups (Table 2; Fig 5; see Figs 2, 3). In 2 patients, 1 in group 1 and 1 in group 3, the postoperative width of the third ventricle was slightly higher than the normal limit (see Fig 3).

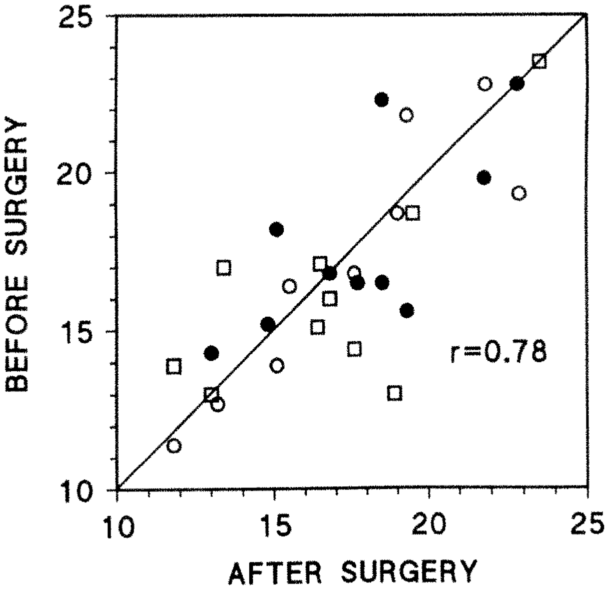

Fig 5. Bicaudate diameter (in millimeters) in 29 patients before and after operation. The coefficient of correlation (r) is calculated. (○ = bubble oxygenator without filter; ● = bubble oxygenator with filter; □ = membrane oxygenator without filter.)

Comment

By virtue of its high sensitivity, MRI offers a new dimension in the assessment of ischemic lesions in the brain [12–14]. However, MRI does not seem to have been used earlier for the study of ischemia in adults undergoing CPB.

In one computed tomographic study [16], the frequency of cerebral infarction in adults after CPB was reported to be 2%. The appearance of 2 cases of postoperative infarction in our group of 29 patients amounts to a frequency of 7%. In both patients, a bubble oxygenator was used, one without and one with an arterial line filter. Obviously, the series is too small to warrant a fair assessment of the rate of ischemic complications. On the other hand, 7% may be a more accurate figure, as small infarcts, like the smallest detected in this study, can be missed by computed tomography, at least in an early stage. The location and distribution of the lesions in this study did not indicate that they were border-zone infarcts (watershed infarcts), which usually appear after episodes of low systemic blood pressure. Instead, they had the appearance of true embolic infarcts in the second- and third-order branches of the posterior cerebral and middle cerebral arteries, respectively.

Table 2. Measurements From Magnetic Resonance Imaging of Brain in 29 Patients[a,b]

	Bubble Oxygenator				Membrane Oxygenator	
	No Filter (n = 9)		Filter (n = 10)		No Filter (n = 10)	
Variable	Preop	Postop	Preop	Postop	Preop	Postop
Frontal horn index	0.26 (0.02)	0.26 (0.03)	0.27 (0.02)	0.27 (0.02)	0.26 (0.02)	0.26 (0.03)
Bicaudate diameter (mm)	16.8 (4.4)	16.2 (3.9)	16.2 (2.5)	16.6 (3.3)	15.1 (3.0)	15.6 (2.9)
Third ventricle diameter (mm)	5.1 (1.8)	5.1 (1.7)	4.3 (1.1)	4.6 (1.3)	4.9 (1.0)	4.3 (1.8)

[a] Data are shown as the mean with the standard deviation in parentheses.

[b] There were no significant differences between the preoperative and postoperative values.

In children, both computed tomography and MRI have been used for the purpose of estimating brain complications after CPB [1, 2]. In one computed tomographic study [2] of children aged 8 months to 10.5 years, postoperative dilatation of the ventricles was noted when a bubble oxygenator and a 40-μm filter were used or when no arterial line filter was employed. The dilatations were not accompanied by any obvious clinical symptoms or signs, and the ventricles were found to have returned to the baseline width in late follow-up examinations. A comparison of ventricular width changes before and after operation showed a significant difference at the 5% level in favor of the fine 20-μm filter group or the membrane oxygenator group. The method used for the assessment of ventricular width was not reported [2].

In another study [1] comprising 15 patients, 11 of whom were 1 year old or less, MRI was used for preoperative and postoperative evaluations of the brain. A widening of the ventricles was seen in the postoperative scan when a membrane oxygenator and a 37-μm arterial filter were used during CPB. Late follow-up examinations were not performed. The authors hypothesized that the atrophylike pattern observed after CPB may be related in some way to microemboli in the brain parenchyma.

It may be true that the infant brain is a more sensitive model for the study of the effects of CPB. However, the immature brain has a higher content of free water than the adult brain, and the brain mass also constitutes a much higher percentage of the total body weight in the infant than in the adult man. From this, it follows that the turnover rate of water in the brain is also higher in infants. These facts probably account for the common observation in pediatric neuroradiology practice that the size of the ventricles can vary within rather wide limits with the nutritional status and the level of body hydration. Therefore, variation in ventricular size in children with heart disease undergoing CPB should not be correlated primarily with the effect of oxygenation or the use or nonuse of filters unless the state of hydration is also considered. This does not seem to be the case in these studies. For this reason, it seems probable that the enlargement of the ventricular system observed in the postoperative period in infants with congenital heart disease is not related to microembolization but rather reflects a change from a high level of hydration of body tissues (including the brain parenchyma) to a low level of hydration.

In adults, the ventricular volume can vary with factors that can be related to the state of nutrition and hydration, but these variations occur at a much slower rate. For instance, in individuals addicted to alcohol, long-term follow-up studies with computed tomography have demonstrated a normalization of the atrophylike pattern observed in a baseline study after prolonged drinking [17, 18]. Furthermore, variations in the size of the cerebrospinal fluid spaces are known to occur in patients on a regimen of steroid therapy [19] and in patients with anorexia [20]. In this study, the observation period was short and the patients, all adults, were not decompensated, nor were they in a poor nutritional state. In 2 patients the value for the transverse width of the third ventricle was slightly higher postoperatively than the adopted limit for normality. However, the changes from the baseline value were small, and for this reason, they were considered clinically insignificant (see Fig 3).

Hyperintense white-matter foci are uncommon in children but occur very frequently in elderly patients [21, 22]. Two different types of such changes can be distinguished in images obtained with a sequence of the type used here, ie, a standard spin-echo sequence with a long repetition time and a short and a long echo (in this case, repetition time of 2,300 ms and echo time of 35 and 120 ms): those with a higher signal than brain parenchyma in both long- and short-echo images and those with signal characteristics more or less identical with cerebrospinal fluid.

The first type is believed to represent one of three different pathological entities: (1) infarction without secondary cavitation, (2) gliosis, and (3) demyelination. The pathophysiological mechanisms behind these changes are still a matter of controversy. However, there seems to be a general consensus that vascular insufficiency caused by degenerative changes in the walls of the penetrating arteries of the brain play an important part in the development of these lesions [23–25]. The second type represents different sorts of fluid-filled spaces such as small brain cysts or diverticuli, cystic degeneration (cavitation) secondary to infarction, and, finally, widened perivascular subarachnoid spaces [23, 24].

Although a more accurate differentiation between the different types can be obtained, it was obvious that the vast majority of these lesions were foci of the first type and to some degree also represented widened perivascular cerebrospinal fluid spaces. These types of lesions are believed not to be caused by acute incidents of ischemia but rather to reflect chronic processes, among which hypertension and other cardiovascular risk factors may be important [26, 27], age being the single factor that most consistently correlates well with the frequency of these changes [22]. In this investigation, the number, extent, and distribution of the white matter abnormalities were found to be remarkably unchanged postoperatively compared with the preoperative findings. This indicates that they were probably of a chronic nature in the patients in this study. Nevertheless, the preoperative and postoperative mapping and analysis of foci of increased T2 signals did not support the hypothesis of the occurrence of a generalized microembolization during CPB.

In conclusion, embolic complications can occur even when an effective arterial line filter is used during CPB. The number of patients in this study proved to be too small to determine the exact value of using any specific method of oxygenation, whether combined with a filter or not. Cerebral infarctions were found in 2 patients postoperatively, both with bubble oxygenator. Magnetic resonance imaging seems to be the method of choice for the evaluation of ischemic complications during CPB.

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Combined Cardiac Operation and Carotid Endarterectomy During Aortic Cross-Clamping

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We present a surgical technique that we believe provides superior cerebral protection for simultaneous correction of carotid and cardiac pathology with low operative mortality and stroke rate. Our study population consists of 23 consecutive patients undergoing cardiac operation between August 1989 and April 1991 who also had associated critical (>85%) carotid artery stenosis. Using 20°C systemic hypothermia for cerebral protection, we performed simultaneous correction of both lesions during the aortic cross-clamp period, using continuous retrograde blood cardioplegia for myocardial protection. Mean patient age was 69.4 years; 83% were 65 years or older. Eighty-seven percent had angina, 35% had recent myocardial infarctions (within 30 days), and 52% had congestive heart failure. Asymptomatic bruit was found in 39%, and 61% had previous strokes, neurologic symptoms, or both. All had 85% or greater luminal narrowing on cerebral angiography, with 65% having severe or critical contralateral disease as well. Sixty-one percent had associated other vascular pathology, including peripheral vascular occlusive disease, renal artery stenosis, or abdominal aortic aneurysm. There were no postoperative strokes or neurologic events. One early vein graft occlusion resulted in postoperative myocardial infarction and subsequent death (4.3%).

(Ann Thorac Surg 1992;53:813–6)

Lowering the incidence of neurologic events in patients with combined cardiac and carotid artery disease has remained a desired goal. Historically, the risk of stroke is substantial when cardiac operation is contemplated in this group of patients. The risk remains whether medical therapy or a variety of surgical strategies is employed for the carotid disease.

We present an operative plan that offers the additional cerebral protection of the deeper hypothermia available during aortic cross-clamping. It is predicated upon the superb myocardial protection provided by continuous cold blood retrograde perfusion, and does not necessitate prolonged pump time for rewarming.

Material and Methods

The carotid artery is exposed through an incision anterior to the sternocleidomastoid muscle. Median sternotomy is made and conduit is harvested. The patient is heparinized and cannulated. If the aorta is free of disease, proximal aortosaphenous anastomoses are constructed before bypass with a partial occlusion clamp. If the aorta is diseased, or for most reoperations, proximal anastomoses are constructed during cross-clamp. Extracorporeal circulation is initiated and established for an average period of 143 minutes (median, 130 minutes; flow range, 1.6 to 2.0 $L \cdot m^{-2} \cdot min^{-1}$). A retrograde cannula is placed in the coronary sinus, and a vent is placed in the ascending aorta. The aorta was cross-clamped an average of 111 minutes (median, 97 minutes). Pulsatile flow is maintained during cross-clamp with a Stockert-Shiley roller pump and a PFC-III controller. Electromechanical arrest is achieved using warm blood retrograde cardioplegia, which is then cooled and given continuously for myocardial protection. Details of this technique have been previously published [1].

As the cardioplegia is cooled, the perfusate temperature is dropped directly to 20°C. The operation proceeds exactly as if cardiac operation alone were being performed. That is, the aorta is opened and the valves are excised and sized if aortic valve replacement is being done, distal anastomoses are begun if myocardial revascularization alone is being performed, or atrial incision is made and the mitral valve is exposed and assessed if mitral valve repair or replacement is to be performed.

Approximately 10 minutes into the cross-clamp time, the perfusionist notifies the surgeon when a bladder temperature of 20°C is reached. Anastomosis is completed, or a convenient stopping place is reached, and the cardiac portion of the operation is stopped. The aortic cross-clamp remains in place, and continuous cold retrograde cardioplegia protects the heart while attention is then turned to the carotid artery. The carotid artery is clamped, opened, and endarterectomized without shunting. Strict adherence to the principles of endarterectomy are observed, including carrying the endarterectomy incision onto normal internal carotid artery distally, endarterectomy of the internal and external carotid arteries, meticulous debridement or tacking of all flaps, and closure of the arteriotomy with a saphenous vein patch using continuous 6-0 nonabsorbable suture. The artery is deaired,

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Table 1. Preoperative Cardiac Status[a]

Findings	No. of Patients	Percentage
Male	16	70
Age >65 years	19	83
Stable angina	6	26
Unstable angina	14	61
Silent ischemia	3	13
MI (<30 days)	8	35
CHF	12	52
EF ≥0.50	15	65
EF 0.35–0.50	6	26
EF 0.20–0.35	2	8
EF <0.20	0	0
Aortic stenosis	1	4
Mitral stenosis	1	4
1-vessel disease	0	0
2-vessel disease	4	17
3-vessel disease	18	78
Left main stenosis	4	17

[a] N = 23; mean age = 69.4 years.

CHF = congestive heart failure; EF = ejection fraction; MI = myocardial infarction.

Table 2. Preoperative Neurologic Status

Findings	No. of Patients	Percentage
Previous stroke		
Asymptomatic critical stenosis	5	21
Contralateral TIAs	3	13
Previous CEA, contralateral TIAs	1	4
New CVA, ipsilateral crescendo TIAs	1	4
No previous stroke		
Asymptomatic critical stenosis	9	39
TIAs	3	13
Vertebrobasilar symptoms	2	8

CEA = carotid endarterectomy; CVA = cerebrovascular accident; TIA = transient ischemic attack.

and flow is reestablished in the carotid artery. Carotid cross-clamp times ranged from 14 to 52 minutes (mean, 27 minutes), with the patient's mean perfusion pressure 50 to 85 mm Hg (mean, 67 mm Hg) during clamping.

At this point the perfusate temperature is raised to 28°C, and the heart operation is resumed. During this time the remaining coronary grafts are completed, or the valve replacement or repair is performed, and the patient's temperature rises to the moderate hypothermia levels used during our routine operations. During the final graft anastomosis, or during closure of the aorta or atria, the patient is rewarmed toward a systemic temperature of 37°C. The rest of the operation is finished in routine fashion, and extracorporeal circulation is discontinued. We have found it useful for blood conservation to maintain a low-speed pump sucker in the heparinized neck incision until heparin is reversed and formal hemostasis can be secured.

Patient Population

The study population consists of 23 consecutive patients undergoing combined carotid and cardiac operation over a 20-month interval from August 1989 to April 1991 at the Lankenau Medical Center, representing 3% of the 763 open heart operations performed by this service during this interval.

In all patients referred for heart operation, detailed neurologic histories were taken, and carotid bruit was sought. The patients whose results were positive were further evaluated by noninvasive carotid Doppler and ultrasound, and those with positive (>70%) test results underwent carotid digital subtraction angiography. Patients with symptomatic bruits went directly to digital subtraction angiography. Critical stenosis was considered to be present if 85% or greater luminal narrowing was detected. Nineteen patients scheduled for heart operation had associated carotid disease.

All patients referred for carotid endarterectomy underwent stress thallium testing and cardiac catheterization if indicated. Four patients scheduled for carotid endarterectomy were found to have associated heart disease.

PREOPERATIVE CARDIAC STATUS. Table 1 lists characteristics of the patients' preoperative cardiac findings. Of the patients with valvular disease, 1 had aortic stenosis in addition to his coronary artery disease, with an aortic valve area of 1.1 cm^2, and one had mitral stenosis without coronary disease, with a mitral valve area of 0.9 cm^2.

PREOPERATIVE NEUROLOGIC STATUS. Table 2 lists characteristics of the patients' preoperative neurologic findings. The 1 patient with acute stroke, new computed tomographic scan defect, and ipsilateral crescendo transient ischemic attacks was treated with heparin for 2 weeks before combined operation.

Cerebral angiography was considered to show a critical lesion if there was 85% or greater luminal narrowing. Table 3 summarizes these findings. Three patients in the group with 85% or greater contralateral disease had 85% or greater stenosis of one or both vertebral arteries as well.

OTHER VASCULAR DISEASE. Thirteen patients (57%) had peripheral vascular occlusive disease, 3 patients had se-

Table 3. Preoperative Cerebral Angiographic Stenoses

No.	Percent	Ipsilateral Carotid	Contralateral Carotid
8	35	>85%	<30%
9	39	>85%	50%–80%
4	16	>85%	>85%
2	8	>85%	Occluded

vere renal artery stenosis, and 3 patients had abdominal aortic aneurysmal disease, for a total of 61% with associated other vascular pathology.

Operations Performed

Of the 23 patients, 22 received coronary artery bypass grafts, including 1 patient who had aortic valve replacement and left ventricular aneurysm repair. Nineteen patients (83%) received internal mammary artery grafts, including 2 patients with bilateral mammary artery grafts and 5 patients with sequential left internal mammary artery grafts. Three patients required endarterectomy of the right coronary system, and 3 patients required endarterectomy of the left anterior descending coronary artery using a long arteriotomy, endarterectomy, and vein patch as described by Johnson and associates [2]. The number of grafts ranged from 2 to 7 (mean, 4.3) per patient.

Results

All patients were followed up preoperatively and postoperatively by a consulting neurologist. Patients were examined the morning after operation and were seen daily by a neurologist until discharge. There were no strokes or neurologic morbidities of any kind during the hospital course.

There was one postoperative death due to multiorgan failure, which was precipitated by a myocardial infarction on postoperative day 3 related to technical factors. There was an additional myocardial infarction on postoperative day 2, which required readmission to the intensive care unit and from which the patient subsequently recovered. There was one episode of low output without myocardial infarction in a patient with ischemic dilated cardiomyopathy, which resolved. The same patient suffered a nonfatal pulmonary embolus before discharge, which also resolved. Three patients were reexplored for postoperative bleeding. Two patients required ventilatory support beyond 72 hours, including 1 who subsequently required reoperation for sternal bone dehiscence. Three patients required permanent pacemaker insertion for indications that existed before the heart operation.

All patients or referring physicians were contacted by telephone at the time of this writing. This represents a 100% follow-up for a period of from 3 months to nearly 3 years. One late death occurred due to toxic epidermal necrolysis. One patient reports moderate progression of his Parkinson's disease. No other patients report new neurologic symptoms or have had neurologic events of any kind.

Comment

The incidence of serious carotid stenosis in patients undergoing open heart operation has been reported to be between 6% and 16% [3]. It is estimated that only 3% of coronary surgical candidates have carotid endarterectomy performed before, during, or soon after cardiac operation [4]. The impetus for this study was our clinical observation, in addition to the well-documented studies of others [5, 6], that the patient with an untreated carotid stenosis suffers a significant postoperative stroke risk.

We consider the patient who awakens from a heart operation with a neurologic deficit to have had an embolic stroke, and not an ischemic stroke from carotid disease. This can occur in the presence or absence of carotid disease, and its incidence has been estimated as 0.7% [5]. We identified this occurrence in 5 of 740 of our patients operated on for heart disease only during this interval, for an incidence of 0.68%.

The results of several studies using electroencephalography [7, 8] and xenon tracers [9, 10], and the absence of this occurrence in this study population with known severe carotid lesions, weigh against the occurrence of the so-called watershed infarct mechanism postulated to occur with the initiation of bypass.

Rather, the untreated carotid stenosis patient may suffer a postoperative stroke subsequent to operation during episodes of hypotension, arrhythmia including atrial fibrillation, or a hypercoagulable state [5]. This risk approaches 3% for an unscreened bruit [5], 6.3% for an asymptomatic severe lesion [6], and 8.7% for a severe symptomatic lesion [11].

Multiple surgical strategies to mitigate this risk have been generated. They include no intervention for asymptomatic critical carotid artery disease [12, 13], staging the procedures at separate sittings as dictated by the individual patient's relative risk of stroke after cardiac operation versus myocardial infarction after carotid operation [11, 14], and several combined procedures. Combined procedures reported have been sequential, with the endarterectomy performed before bypass [15], and synchronous, using a two-team or single-surgeon approach on bypass [16–18].

The groups reporting endarterectomy on bypass have all performed endarterectomy before cross-clamping with the heart beating or ejecting. This allows systemic temperature to be lowered only to the 28° to 32°C range, lest the heart fibrillate. We believe additional cerebral protection is available by cross-clamping and taking the systemic temperature down to 20°C.

Studies have shown that 20°C hypothermia reduces cerebral oxygen consumption by 80% [19]. Oxygen delivery, as shown by cerebral blood flow measurements, has been preserved on cardiopulmonary bypass despite the presence of carotid disease [9], and in a separate study down to pressures of 30 mm Hg [20]. These studies were designed to define the safe lower limits of whole body flow, but we see no reason not to apply these findings to normal whole body flows with low regional blood flow with the carotid cross-clamp on.

We postulate the following advantages to this technique: (1) protection from ischemic strokes during the endarterectomy when the carotid artery is clamped, (2) obviating the necessity of inserting a shunt with its attendant risks, (3) allowing the carotid artery to be clamped and unclamped under conditions of lowered pressure and flow, which may be less likely to dislodge an embolus, (4) allowing adequate time to perform long arteriotomy up into normal carotid artery and long patch closure to prevent intimal flap occlusions.

Presently, using the previously available surgical strategies, the operative stroke rate is equal to or greater than that of medical management in patients with asymptomatic critical carotid disease seen for heart operation in the short term. Endarterectomy may still be performed because of the long-term benefits. Symptomatic patients who are seen for heart operation are most often operated on, but because of their advanced disease they have a high stroke rate and high mortality with present strategies [11]. The problem appears to be how to provide optimal protection to both organs when carotid and cardiac pathology coexist.

The size of this series is relatively small; however, no patient was excluded because of the degree of severity of the clinical situation, complexity of the cardiac operation, or the cerebral vessel anatomy. There were no strokes in this series, and we attribute this to greatly improved cerebral protection. The relatively high rate of postoperative reexploration for bleeding (3/23 = 13%) is noted and may be related to 20°C cooling. This technique has substantially reduced the incidence of postoperative carotid stroke in our practice. If further experience bears out the preliminary results, then the concept of using the heart-lung machine to protect the brain during endarterectomy will support aggressive surgical intervention to improve the management of this difficult problem.

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Rounded Atelectasis: A Pulmonary Pseudotumor

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Rounded atelectasis is a benign entity that is often misinterpreted as a pulmonary neoplasm. The roentgenologic appearance of a mass is due to an infolding of atelectatic tissue intermingled with pleura, blood vessels, and bronchi. Rounded atelectasis is usually asymptomatic and is commonly associated with chronic pleural disease or pleural effusions. The distinctive radiologic features include a rounded, pleural-based opacity associated with adjacent pleural thickening and volume loss of the affected lobe. The pathognomonic sign is the "comet tail" that results from the crowding of vessels and bronchi as they enter the atelectatic region. Many authors consider this constellation of findings diagnostic. Rounded atelectasis usually remains stable over time; however, slow growth, as well as diminution in size, has been described. A retrospective analysis revealed 7 cases of rounded atelectasis at our institution over a 9-year period. Three were operated on to exclude malignancy, one was confirmed at operation performed for other reasons, and 3 were followed up expectantly. We conclude that recognition of this entity and its radiologic features can be diagnostic and render further workup, including thoracotomy, unnecessary.

(Ann Thorac Surg 1992;53:817–21)

Peripheral pulmonary masses may require thoracotomy for diagnosis. In certain instances, however, classic radiographic findings may preclude thoracotomy. These include the typical popcorn calcifications of a hamartoma, documented stability of a lesion for 2 years, and angiographic findings of an arteriovenous malformation. To this short list we suggest the addition of rounded atelectasis (RA).

Rounded atelectasis, also known as folded lung syndrome, Blesovsky's syndrome, shrinking pleuritis with atelectasis, atelectatic pseudotumor, and pleuroma, is a form of peripheral atelectasis that presents radiographically as a pulmonary mass. Familiarity with the entity of RA will diminish the likelihood of unnecessary exploratory thoracotomy. Subsequent to the initial description of RA in 1966 [1], its radiologic features have been well delineated [2–5]. Today, many authors agree that the diagnosis can be made by these distinctive features and no further workup is necessary [5–9]. Herein, we report our institution's experience with 7 cases of RA and review the literature.

Material and Methods

A retrospective review of all computerized chest radiography reports at Thomas Jefferson University Hospital for the years 1982 through 1990 was performed. This yielded 14 patients in whom RA was included in the differential diagnosis of a pulmonary opacity. Four of these patients underwent thoracotomy and had the diagnosis of RA confirmed. Of the remaining 10, 3 had convincing radiographs, combined with sufficient clinical and radiographic follow-up, to be classified as having RA; the remaining 7 were excluded.

Results

Patient 1, an 81-year-old man with possible silica exposure, had a right pleural effusion and shortness of breath. Computed tomography, bronchoscopy, and percutaneous needle biopsy of a right lower lobe mass (Fig 1), were nondiagnostic. As he was suspected of having malignancy, he underwent thoracotomy. At operation no mass was palpated; however, at the site of the radiographic abnormality there was a thick visceral pleural plaque. Pleural and lung biopsies were followed by regional decortication with successful reexpansion of the underlying atelectatic lung. Histologic evaluation revealed thickened visceral pleural plaque with minimal nonspecific inflammation. A follow-up chest roentgenogram 3 months later was free of active disease.

Patient 2, a 69-year-old man, was being followed up for clinically significant asbestosis. Serial radiographs suggested a slight increase in the size of a left lower lobe opacity over 14 months (Fig 2). At thoracotomy to exclude malignancy, diffuse pleural thickening was found, most pronounced at the site of the opacity. No mass was palpable. A wedge resection in the area corresponding to the shadow revealed benign pleural plaque with underlying atelectatic, fibrotic parenchyma with ferruginous bodies.

Patient 3, a 66-year-old man with a history of tobacco use and repeated episodes of congestive heart failure, had an unchanged peripheral left lower lobe opacity for greater than 1 year which was presumed to be RA. During placement of an internal defibrillator, RA was confirmed, characterized by a thickened visceral pleural plaque with

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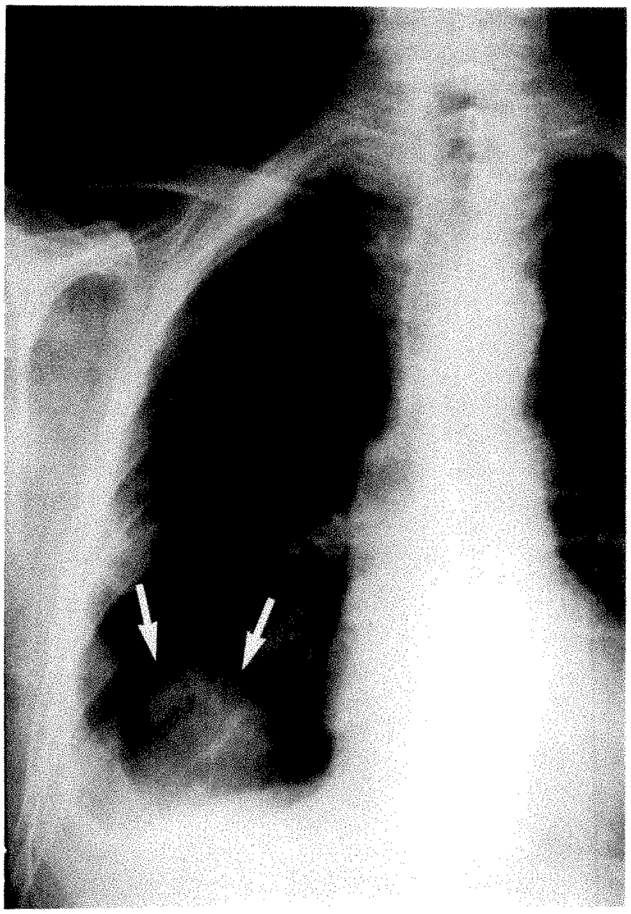

Fig 1. (Patient 1.) Rounded atelectasis of the right lower lobe (arrows).

underlying atelectatic lung. Biopsy revealed fibrous pleural plaque with minimal inflammatory infiltrate.

Patient 4, a 58-year-old woman with a history of tobacco use, had right-sided pleuritic chest pain. Chest roentgenogram and computed tomography revealed a right lower lobe pleural-based opacity. Bronchoscopy and percutaneous needle biopsy were nondiagnostic. At thoracotomy to exclude malignancy, pleural thickening and adhesions were found, but no mass. Pleural and lung biopsies were followed by limited decortication, which was successful in reexpanding the underlying lung. Pathology revealed chronic pleural inflammation.

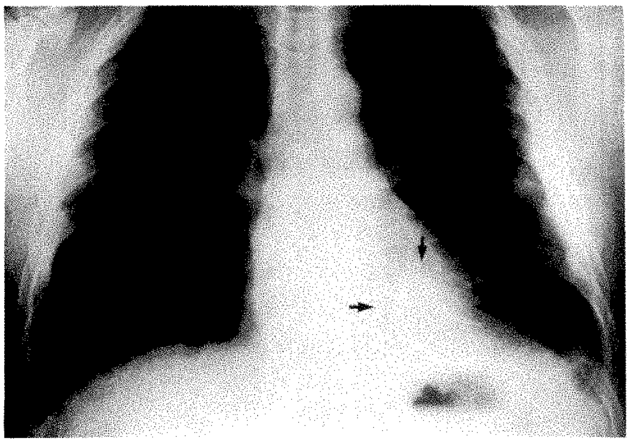

Fig 2. (Patient 2.) Left lower lobe rounded atelectasis (arrows).

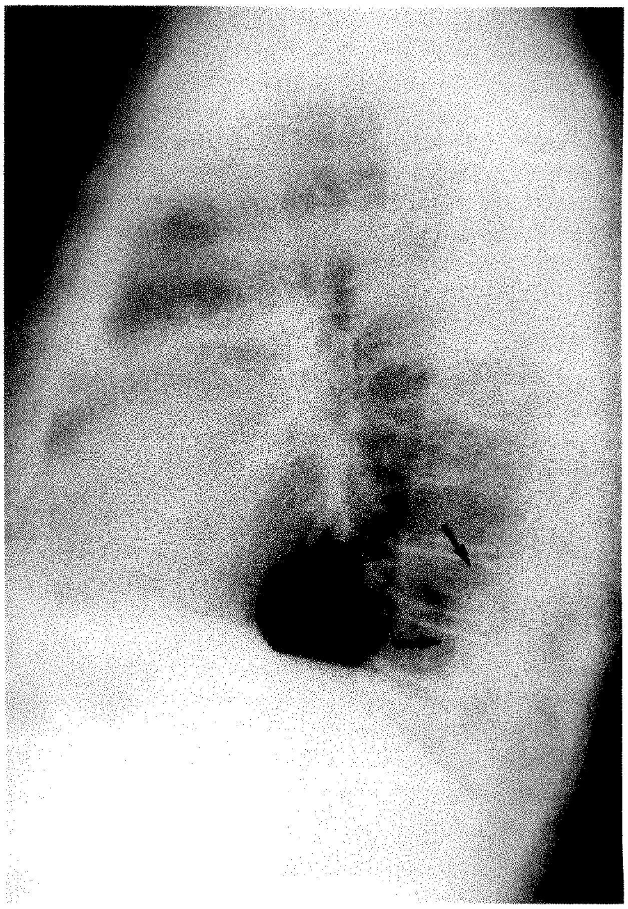

Fig 3. (Patient 5.) Typical posterior, inferior location of rounded atelectasis (arrows).

Patient 5, a 50-year-old man being followed up for clinically significant asbestosis, had an unchanged left lower lobe opacity for at least 5 years (Fig 3).

Patients 6, an 83-year-old man, and 7, a 92-year-old man, both with a history of tobacco use, had chronic relapsing pleural effusions from congestive heart failure. In addition, patient 6 had procainamide-induced lupus with pleuritis. Both had opacities of the right lower lobe, and over follow-up periods of 1½ and 2 years, respectively, the shadows of presumed RA remained unchanged.

Comment

In 1966 Blesovsky [1] reported 3 cases of "lung folding" in association with large pleural plaques. All 3 cases were found at thoracotomy to have localized visceral pleural thickening with "folded" underlying lung but no mass. The lung was successfully expanded by regional decortication. In 1971 Hanke [10] introduced the term round atelectasis. He accumulated 22 cases of RA all due to exudative tuberculous pleurisy. None of these patients underwent thoracotomy. In 1980 Schneider and associates [6], in the first American publication, reported 5 patients. Before they were aware of the entity, 2 of their 5 patients underwent thoracotomy; however, 3 subsequent patients were followed up nonoperatively. Increasing familiarity with the lesion has resulted in numerous publications concerning the clinical presentation, radiographic diagnosis, natural history, and treatment of RA.

The pathogenesis of RA remains controversial. Hanke [10] and later Kretzschmar [11] postulated the following sequence of events. A pleural effusion will cause partially aerated lung to float on the effusion. If the rate of effusion formation is greater than the rate of alveolar air resorption, a cleft or groove will form on the visceral pleural surface and the lung may then tilt on this cleft. The lung then curls on itself in a concentric fashion, increasing in size as the effusion grows. Chronicity or a high fibrin content of the effusion causes adhesions to form between the apposed pleural surfaces, thus fixing the atelectatic lung. Pleural thickening that later bridges the cleft helps to sustain the collapsed segment. This process usually involves cranial tilting of the lower lobes, causing the shadow to present posteriorly. Less commonly, the lower lobe can tilt caudally, with the lesion then presenting as a diaphragmatically based mass. The lesions can also involve the upper and middle lobes, consequently presenting anywhere in the thorax. This theory is corroborated by Smith and Schillaci [12], who describe the development of RA in a patient with a parapneumonic effusion. After resolution of the effusion the RA decreased in size and completely disappeared by 3-months' follow-up.

An alternate theory was later postulated as Schneider and associates [6] noted that none of their 5 patients, and relatively few in the literature, had documented free pleural fluid before the development of RA. In the majority of published cases, RA is associated with chronic pleural disease, particularly that due to asbestos exposure. Dernevik and co-workers [13], in presenting 28 patients, of whom 21 had asbestos exposure, renamed the entity shrinking pleuritis with atelectasis. They proposed that repeated pleural irritants such as tobacco, asbestos, and silica caused a localized visceral pleural reaction with the formation of a pleural plaque. Subsequent pleural shrinkage caused the development of atelectasis in the underlying parenchyma, which assumed a rounded configuration. Histologic evaluation revealed thickened visceral pleural plaque with numerous fibrous fascicles of visceral pleura extending into the atelectatic segment. Menzies and Fraser [14] examined eight pathologic specimens. They found the same pathology, with invaginations of pleura up to 2 cm deep. In no case was a single cleft found. Of our cases, 3 can be ascribed to chronic pleural disease secondary to pleural irritants alone (patients 2, 4, and 5) and 4 to pleural irritants combined with repeated pleural effusions (patients 1, 3, 6, and 7).

Many authors now favor the shrinking pleuritis theory. However, it is apparent that the etiology of RA is multifactorial, and it can result from either chronic pleural thickening or effusion.

The incidence of RA is impossible to quantitate, but it is not rare. Since Blesovsky's report in 1966, approximately 250 cases have been reported in the literature. At our institution RA was considered in the differential diagnosis of 12 patients over a 9-year period. As the entity becomes more widely known, the diagnosis will be made with increasing frequency.

Combining our 7 cases with the reviewed literature [1–9, 12–27], RA has been described in patients from 20 to 92 years of age. Eighty percent are male, and 65% give a clear history of asbestos exposure. Tobacco use is very common. In those patients with a pleural effusion, often the cause is not determined. Documented cases of RA have followed parapneumonic effusions, congestive heart failure, Dressler's syndrome, pulmonary infarcts, and tuberculous effusions. Rounded atelectasis is almost always asymptomatic, being discovered on chest roentgenograms taken for other reasons. Payne and colleagues [16] described 3 patients with persistent nonpleuritic chest pain. Two of the 3 were asymptomatic after successful decortication, whereas the third had continued pain after unsuccessful reexpansion. Physical examination will be nonspecific.

The key to diagnosis of RA is its radiologic features. On plain chest radiographs there will be a round to oval pleural-based shadow ranging from 2.5 to 7 cm in diameter. There is a sharp angle between the shadow and the pleura, confirming its parenchymal location. Its edges may be sharp or indistinct, but all will have blurring of at least one margin where vessels and bronchi enter the RA. There may be an air bronchogram within the shadow, most commonly where the bronchovascular bundle enters. Eighty percent of published cases are in the posterior lower lobes. Rounded atelectasis can be bilateral. There may be pleural thickening, including the interlobar fissure, which will be most severe at the site of the shadow. There will be volume loss of the affected lobe with compensatory hyperaeration of the remaining lung. There may also be pericardial or pleural tenting, thus demonstrating that the lesion is retractile and not expansive (see Figs 1–3).

The most crucial radiologic feature of RA is the "vacuum cleaner effect," known more commonly as the "comet tail." As the section of lung collapses it will crowd its bronchovascular bundle together and pull it into the region. The majority of cases involve cranial tilting of the lung and, therefore, the comet tail will extend from the hilum toward the base of the lung and then sweep upward to enter the inferior pole of the shadow. In the less common caudal or horizontal tilting the comet tail will be seen to sweep into the superior and medial or lateral poles, respectively.

Computed tomography confirms the plain film findings and is more sensitive for volume loss, the extent of pleural disease, air bronchograms, pulmonary fibrosis, and, most importantly, the comet tail (Fig 4). This crowding of bronchovascular bundles can be seen entering the shadow from several sides, demonstrating the "talon

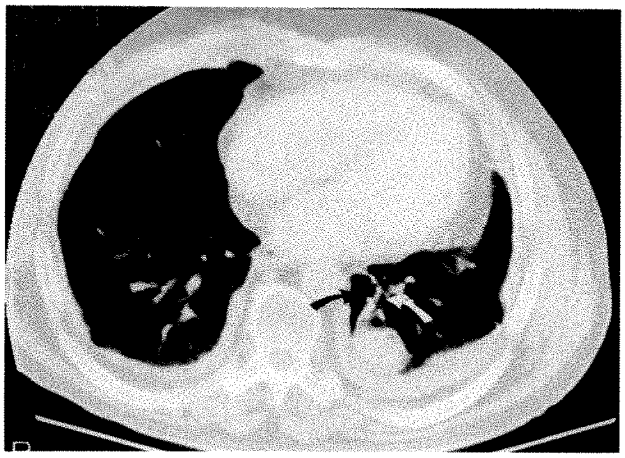

Fig 4. (Patient 2 [same patient as in Fig 2].) Computed tomography of 3.5-cm pleural-based mass. Note volume loss on the left, pleural thickening, and the comet tail (arrows).

sign" [9]. Rounded atelectasis will usually enhance with intravenous contrast medium; however, this is also true of some carcinomas and is, therefore, unreliable as a differentiating sign. Furthermore, Tylen and Nilsson [17], in performing computed tomography on 12 patients, found unsuspected bilateral lesions in 2. Lateral tomography is considered by some authors to be more sensitive that computed tomography for the comet tail [8, 16].

In equivocal cases invasive methods have been used. Bronchoscopy will be unremarkable in RA. Bronchography [6, 11, 17, 19] and arteriography [15, 18] would reveal sweeping of bronchi and vessels, respectively, toward the opacity. However, their associated morbidity preclude their routine use.

Fine-needle aspiration biopsy is a safe procedure in patients with RA given the subpleural fixed position. However, its utility is limited because malignancy cannot be excluded with a negative result. Sinner [15] evaluated 55 patients with fine-needle aspiration biopsy. Five malignant tumors were found with no false positives. He recommended fine-needle aspiration biopsy in equivocal cases, suggesting that a 1% to 2% false-negative rate should be expected. As in 2 of our patients, unless returned as malignant, the results of fine-needle aspiration biopsy will be nonspecific.

No specific treatment is needed for RA. If it is diagnosed at operation, regional decortication will be successful in greater than 90% of cases. After decortication, recurrence of the RA is rare but has been described [6]. Only the very rare patient who has a large atelectatic segment believed to be compromising respiratory function should undergo thoracotomy explicitly for decortication.

When followed up with serial chest roentgenograms, the majority of opacities will remain stable. Some will decrease in size as well as completely disappear. This resolution has been seen to occur over weeks to years [2]. Minimal enlargement of a lesion has been rarely described, as in 1 of our patients; however, this occurs over an extended period of time, much longer than the doubling time of a malignant process.

In conclusion, if a patient has a peripheral pulmonary shadow and RA is suspected, computed tomography should be performed. If the radiologic pattern is typical of RA, we believe the diagnosis can be made with confidence and no further workup is necessary. These patients should have follow-up chest films every 3 months for the first year and every 6 months thereafter. Any major growth in a reasonable amount of time should immediately be suspect and further evaluation performed. In equivocal cases, if the patient is a good operative risk we would proceed to thoracotomy. In a poor-risk patient, lateral tomography, selective bronchography, or angiography could be used to strengthen the diagnosis. Fine-needle aspiration biopsy could also be used in this situation and, if positive, mandate operation or direct nonoperative treatment. If negative, the patient could be managed expectantly.

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Notice From The Society of Thoracic Surgeons

New Poster Session at STS Annual Meeting

The Program Committee of The Society of Thoracic Surgeons has added a Poster Session to the Twenty-ninth Annual Meeting, which will be held at the San Antonio Convention Center in San Antonio, Texas, January 25–27, 1993. Abstracts may be submitted for the Scientific Session, the Poster Session, or either session using the regular abstract form published elsewhere in this issue and also available from the STS headquarters, 401 N Michigan Avenue, Chicago, IL 60611 (telephone: (312) 644-6610).

Be sure to identify in the designated area the session for which the abstract is being submitted. Presenters will be responsible for developing their poster displays. Details on poster specifications will be furnished after acceptance.

Response to Heparinization in Adults and Children Undergoing Cardiac Operations

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The activated clotting time is an unreliable index of anticoagulation status during cardiopulmonary bypass procedures. However, modern instrumentation (Hemotec Hepcon HMS) now allows the monitoring of free heparin levels via automated protamine titration. In the present study, the standard procedure of anticoagulation at Killingbeck Hospital, Leeds, was investigated. Twenty-two pediatric patients and 20 adult patients undergoing open heart procedures involving cardiopulmonary bypass were given empirical doses of heparin (3 mg/kg body weight bolus), and activated clotting time was maintained at a level greater than 450 seconds using the Hemochron Timer. Heparin neutralization was performed at the termination of the bypass period using an empirical equivalent (3 mg/kg) of protamine sulfate. Mean free heparin concentration (± standard deviation) fell from 2.26 (±0.45) mg/kg to 1.39 (±0.34) mg/kg over the period 10 to 40 minutes on bypass in children. In adults, free heparin level declined from 2.56 (±0.58) mg/kg to 1.81 (±0.58) mg/kg over the same period. The biological half-life for heparin was 60 minutes in adults and 35 minutes in pediatric patients. Empirical protamine dosing resulted in excess protamine administration when compared with Hepcon titrated dose requirements: for children: median (range), 80 (12 to 350) versus 33 (12 to 97) mg, $p < 0.001$; and for adults: 350 (200 to 500) versus 130 (61 to 237) mg, $p < 0.001$. In conclusion, empirical heparin administration (3 mg/kg) does not result in "steady-state" anticoagulation during cardiopulmonary bypass, and empirical administration of protamine takes no account of interindividual differences in heparin sensitivity and biological half-life, which may be assessed using the Hepcon HMS.

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Procedures involving cardiopulmonary bypass (CPB) provide the requirement for appropriate anticoagulation. Current practice is to use heparin, as its instant action and amenable neutralization with protamine sulfate make it the anticoagulant of choice [1]. However, alternative anticoagulants (eg, Ancrod) have been suggested, although their use has been restricted mainly to research procedures in animals [2].

The use of heparin in surgery has become associated with simple empirical protocols with dosing based on body weight and surface area [3]. Recent evaluation, however, suggests that these protocols may result in either excessive or inadequate anticoagulation, often going unrecognized until the early postoperative period [4]. Furthermore, assessment of anticoagulant status during CPB using the activated clotting time (ACT) [5] has been widely criticized for failing to reflect circulating free heparin concentration [6] and for being influenced by additional factors such as hemodilution and temperature [7].

The aims of the present study were to assess the appropriateness of current anticoagulation management at the Regional Cardiothoracic Centre, Killingbeck Hospital, Leeds, where an empirical heparin dosing protocol (3 mg/kg body weight) is routinely used during CPB procedures. Comparisons were made between cohorts of adult and pediatric patients undergoing open heart procedures. Repeated measurements of blood free heparin concentration and ACT were performed. In addition, assessment of protamine neutralization of heparin via an empirical method was investigated.

Material and Methods

Twenty-two pediatric patients and twenty adults (Table 1) undergoing consecutive open heart procedures (Table 2) were investigated. The standard anticoagulation practice of heparin administration was studied (ie, 3 mg heparin/kg body weight), and measurements of ACT and free heparin levels were performed at 20-minute intervals using the Hepcon HMS (Hemotec, Inc, Englewood, CO). In addition, conventional anticoagulation monitoring using the Hemochron ACT timer (International Technidyne Corp, Edison, NJ) allowed maintainance of ACT values at the widely regarded safe level of greater than 450 seconds for standardization. Routine laboratory investigations were performed preoperatively and postoperatively to determine changes in hematological and biochemical variables.

Perfusions were accomplished using a membrane oxygenator (Cobe VPCML Labs Ltd, Gloucester, UK) using a flow rate in the range of 1.8 to 2.4 L/m^2 body surface area/min. Arterial oxygen partial pressure was used to

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Table 1. Clinical Characteristics of Patients Undergoing Open Heart Operations[a]

Variable	Adults (n = 20)	Children (n = 22)
Sex ratio	19M:1F	11M:11F
Age (y)	57.3 (37–71)	4.9 (0.1–16.0)
Weight (kg)	79 (58–98)	17.3 (3.2–66)
Height (cm)	172 (163–180)	101 (49–176)

[a] Results are expressed as mean (range).

maintain oxygen saturation between 0.95 and 1.00. Median prime volume was 900 mL (range, 650 to 2,500 mL) in children and 1,800 mL (range, 1,700 to 2,200 mL) in adults. The respective heparin prime used was 3,000 U (range, 2,000 to 6,000 U) in children and 5,500 U (range, 5,000 to 6,000 U) in adults.

The Hepcon HMS was used solely to monitor current practice prior to a future study using the instrument to direct anticoagulant therapy. At termination of bypass, residual free heparin was reversed using protamine sulfate empirically equivalent to that of the initial heparin bolus given (1:1, 3 mg/kg).

Mean duration of extracorporeal circulation was 74 minutes (range, 34 to 137 minutes) in children and 89 minutes (range, 77 to 216 minutes) in adult patients.

Functional Characteristics of Hepcon HMS

The Hepcon HMS provides rapid and precise information as to the (1) in vitro response to heparin via the heparin dose response, (2) heparin calculation (1 mg = 100 USP) based on dosing protocol, patient blood volume (Allen equation [8]), and extracorporeal circuit variables, (3) simultaneous quantitative and functional evaluation of heparin via the heparin assay and HR-ACT, (4) calculation of additional heparin required to maintain the patient at an adequate heparin concentration, and (5) protamine dose needed to reverse heparin.

Table 2. Open Heart Procedures Performed

Type of Operation	No. of Patients
Adults	
Coronary artery bypass grafting	
×2	6
×3	8
×4	2
Aortic valve replacement	2
Mitral valve replacement	2
Children	
Ventricular septal defect	5
Atrial septal defect	7
Total anomalous pulmonary venous drainage	2
Tetralogy of Fallot	4
Transposition of the great arteries	1
Atrial and ventricular septal defects	2
Right ventricular outflow tract obstruction	1

The heparin assay test uses the principle of heparin/protamine titration to quantitatively determine the concentration of heparin in the sample. Each channel of the four-channel cartridge contains a different amount of protamine with a constant amount of thromboplastin for activation of the test. The channel that most closely neutralizes the heparin in the sample is the first to clot.

The activated clotting time (HR-ACT using kaolin as activator) evaluates heparin anticoagulation and is dependent on other factors affecting intrinsic clotting such as platelet function, hemodilution, and hypothermia.

The heparin dose response test is a modified HR-ACT which measures the in vitro anticoagulant response to a known concentration of heparin. The heparin dose response test measures clotting time in response to the addition of 1.5 and 2.5 units of beef lung heparin per milliliter of blood. This response can be used to screen patients for potential resistance/sensitivity to heparin. It can also be used to estimate a minimum heparin dose required to achieve the desired target clotting time.

Blood Sampling

Blood sampling consisted of the drawing of 5.5 mL of blood (3 mL into a syringe designed specifically for the Hepcon HMS and 2.5 mL into a syringe for the Hemochron ACT instrument) from the central venous line. Residual flush solution was cleared before sampling, unused blood being immediately returned to the patient. Specimens were obtained after induction of anesthesia, 10 minutes after heparinization, 10 minutes after the institution of CPB, and every 20 minutes thereafter on CPB. Further sampling was performed 10 minutes after the administration of protamine. Samples taken during CPB were obtained from the pump.

Statistics

Nonparametric data were analyzed using the Mann-Whitney U test for unpaired values and the Wilcoxon test for paired data. Correlations were assessed using the Oxstat (Wight Scientific, London, UK) correlation program. The χ^2 test was used to assess differences in prevalence.

Results

The in vitro dose response to heparin indicated that of the 22 pediatric patients studied 8 exhibited resistance (suggested heparin required, >3.5 mg/kg body weight) whereas 1 patient was sensitive to heparin (<2.5 mg/kg). Of the 20 adults studied, 4 displayed resistance whereas 7 were sensitive to heparin. The heparin dose response ranged from 2.2 to 4.9 mg/kg (mean, 3.3 mg/kg) in children and from 2.1 to 4.5 mg/kg (mean, 3.0 mg/kg) in adults.

Preoperatively, the mean (± standard deviation) baseline HR-ACT was 124 (±9) seconds in children and 134 (±20) seconds in adults. The changes in ACT as determined by the Hepcon HMS and Hemochron timer during

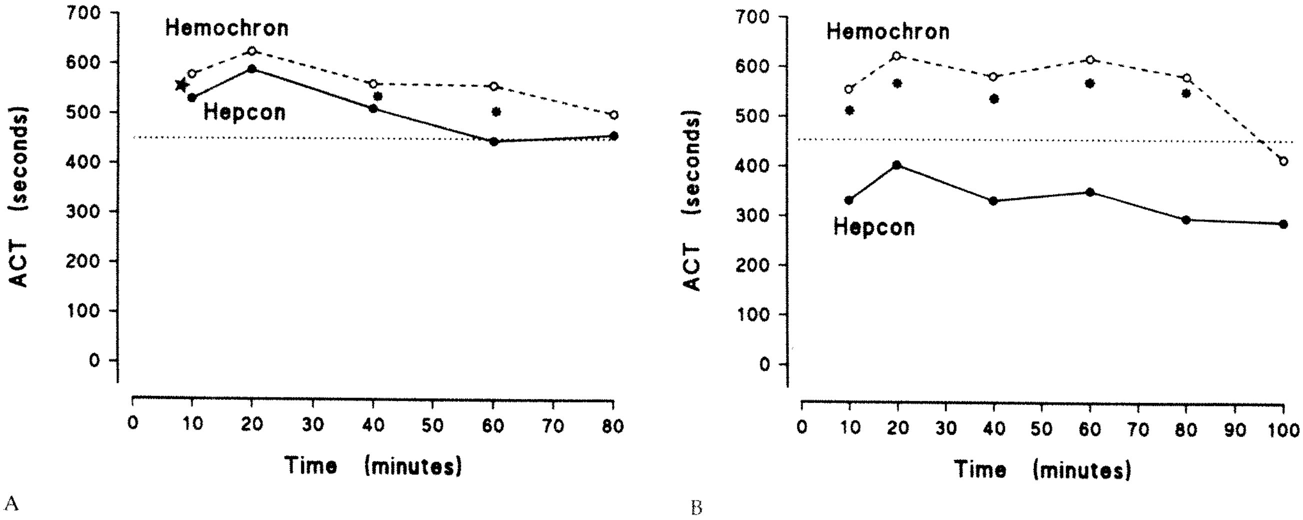

Fig 1. Comparison of Hemochron and Hepcon activated clotting time (ACT) *with time (refer to Table 3 for analysis): (A) adults, (B) pediatric patients. (*p < 0.01 at each interval, 0 to 80 minutes.)*

bypass are summarized in Figure 1. The significance of the differences in ACT values with time are summarized in Table 3. The changes in free heparin levels with time on bypass are shown in Figure 2, with free heparin concentration differing significantly ($p < 0.05$) between adults and children at 40 minutes on bypass. There was a weak but significant correlation between HR-ACT and heparin concentration in both children ($y = 1.34 + 0.001863t$, $r = 0.36$, $p < 0.01$) and adults ($y = 0.75 + 0.002402t$, $r = 0.42$, $p < 0.001$). In children, the initial biological half-life for heparin (ie, time for heparin concentration to fall to 1.5 mg/kg) was approximately 35 minutes compared with 60 minutes in adults.

Free heparin concentration declined rapidly during CPB in the presence of predominantly "acceptable" (>450 seconds) Hemochron ACT values (>90% of measurements). In contrast, low free heparin concentration was associated with a much greater prevalence of unacceptably low HR-ACT determinations: 76% in children and 30% in adults; this difference in prevalence between adults and children was highly significant on χ^2 analysis ($\chi^2 = 33.6$, $p < 0.001$).

The empirical neutralization dose of protamine used was 3 mg/kg in all cases (children: median, 80 mg; range, 12 to 350 mg; adults: median, 350 mg; range, 200 to 500 mg). In both instances the protamine administered was significantly greater ($p < 0.001$) than the Hepcon HMS titrated dose suggested (children: median, 33 mg; range, 12 to 97 mg; adults: median, 130 mg; range, 61 to 237 mg). The differences in titrated protamine dose compared with empirical dose may be accounted for by the decline in free heparin levels with increased time on bypass.

Twenty-four-hour postoperative mediastinal chest drainage was (mean [range] 868 [333–2200] mL in adults and 240 [55–939] mL in children.

Comment

Previous studies have demonstrated that heparin sensitivity and clearance rate (heparin half-life) may vary considerably between patients during CPB [9, 10]. Bull and associates [1] found that given the patient's age, weight, and surface area it was not always possible to predict the required heparin dose needed to prolong clotting time to an arbitrary value or indeed to determine heparin degradation rate, these factors showing threefold and fourfold variations, respectively, between individu-

Table 3. Comparison of the Change in Activated Clotting Time Values With Time Using Hepcon and Hemochron System[a]

	Adults (n = 20)		Children (n = 22)	
Time on bypass (min)	Hepcon ACT (s)	Hemochron ACT (s)	Hepcon ACT (s)	Hemochron ACT (s)
10	529 (371–771)[b]	577 (371–1698)	329 (189–885)[c]	551 (307–1610)
20	587 (330–790)	623 (491–974)	400 (298–999)[d]	615 (407–2500)
40	509 (299–635)[e]	558 (439–1083)	328 (239–892)[e]	572 (410–800)
60	446 (311–657)[e]	555 (431–715)	347 (182–554)[e]	610 (397–1098)
80	459 (274–839)	500 (410–594)	291 (218–362)[e]	570 (380–953)

[a] Results are expressed as median (range). [b–e] Wilcoxon paired *t*-test: [b] $p < 0.05$; [c] $p < 0.005$; [d] $p < 0.001$; [e] $p < 0.01$.

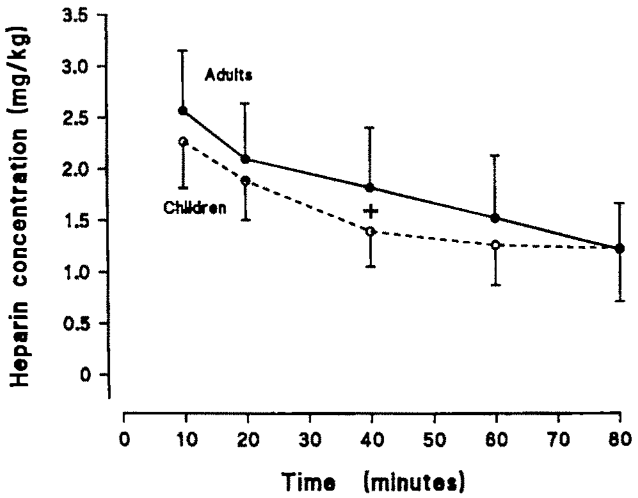

Fig 2. Comparison of the changes in free heparin levels with time on bypass. ($^+p < 0.05$ for difference between adults and children.)

als. It has therefore been suggested that heparinization of patients undergoing CPB operations should be done according to an individualized protocol rather than an empirical protocol [11].

In the present study, it was observed that in both adults and children the in vitro response of patients' blood to heparin varied by more than twofold. This observation was in agreement with that of Akl and co-workers [12]. Similarly, the observed difference in patients' response to heparin between the pediatric and adults age groups has been previously reported by other workers [12–14]. These observations would seem to suggest that the requirement for heparin in pediatric patients exceeds that of adults in achieving a similar level of anticoagulation as assessed by ACT.

The changes in free heparin concentration observed with increasing time on bypass suggest that, in accordance with the findings of a previous study, free heparin concentration declines more rapidly in children than in adults [12]: It has been suggested that this observation may be a result of a higher blood volume/body weight ratio and a higher metabolism rate in children. In the present study it was not possible to determine which, if either, of these factors had the greater impact on heparin levels, or indeed whether additional indeterminate variables played a role in altering free heparin levels in adults and children.

Throughout the bypass period, the Hemochron ACT seldom (<10% of occasions) fell below the "acceptable" value for anticoagulation (450 seconds). However, it was noted with interest that the decline in free heparin levels was associated with a much greater prevalence of "unacceptable" HR-ACT values. These observations suggest that the HR-ACT (Hepcon HMS) may be more sensitive in detecting heparin-induced anticoagulation than the Hemochron ACT. In addition, the susceptibility of the Hemochron ACT to effects of hemodilution and hypothermia (as reported extensively by others [15, 16]) may be much greater than that of the HR-ACT. With respect to the effects of hypothermia, it has been reported [15] that whereas the Hemochron can maintain a temperature of 37°C, the ability of this instrument to raise rapidly a 2-mL blood sample from 25°C to 37°C is limited. Using this instrument it was demonstrated that 5 minutes is required to raise the temperature of water from 25°C to 37°C. During this time, coagulation will be delayed, thereby increasing the ACT. In contrast, the HR-ACT works on a smaller sample volume (0.4 mL) with a consequent ability to raise the temperature of such a sample much more rapidly, thus potentially limiting the effect of hypothermia as a confounding variable.

The empirical method of neutralization of heparin using protamine sulfate has been repeatedly criticized over the last 25 years as being inappropriate, potentially leading to hazardous overadministration with cardiovascular and pulmonary side effects [14, 17, 18]. In the current study, we found that empirical neutralization of heparin with a bolus equivalent of protamine resulted in excessive protamine administration in both adults and children when compared with Hepcon HMS-titrated protamine requirements. In adult and pediatric patients empirical protamine administration resulted in a greater than twofold excess of protamine being administered. This observation closely agrees with the findings of Jobes and associates [19], who reported a 40% decreased need for protamine when in vitro heparin titration was used to determine protamine dose. Similarly, the fixed-dose administration of protamine takes no account of the interindividual differences in heparin sensitivity and half-life, which may be assessed using the Hepcon HMS.

In conclusion, the use of the Hepcon HMS heparin/protamine titration system would seem to convey a number of advantages for individualizing anticoagulation management during CPB in both adults and children. Further studies are indicated to assess the advantages and disadvantages of Hepcon HMS-guided therapy during CPB.

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Warming During Cardiopulmonary Bypass Is Associated With Jugular Bulb Desaturation

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The objective of this study was to characterize cerebral venous effluent during normothermic nonpulsatile cardiopulmonary bypass. Thirty-one (23%) of 133 patients met desaturation criteria (defined as jugular bulb venous oxygen saturation ≤50% or jugular bulb venous oxygen tension ≤25 mm Hg) during normothermic cardiopulmonary bypass (after hypothermic cardiopulmonary bypass at 27° to 28°C). Cerebral blood flow, calculated using xenon 133 clearance methodology, was significantly ($p < 0.005$) higher in the saturated group (33.7 ± 10.3 mL · 100 g^{-1} · min^{-1}) than in the desaturated group (26.2 ± 6.9 mL · 100 g^{-1} · min^{-1}), whereas the cerebral metabolic rate for oxygen was significantly lower ($p < 0.005$) in the saturated group (1.28 ± 0.39 mL · 100 g^{-1} · min^{-1}) than in the desaturated group (1.52 ± 0.36 mL · 100 g^{-1} · min^{-1}) at normothermia. The arteriovenous oxygen difference at normothermia was lower in the saturated group (3.92 ± 1.12 mL/dL) than in the desaturated group (5.97 ± 1.05 mL/dL). Neuropsychological testing was performed in 74 of the 133 patients preoperatively and on day 7 postoperatively. There was a general decline in mean scores of all tests postoperatively in both groups with no significant difference between the groups. We conclude that cerebral venous desaturation represents a global imbalance in cerebral oxygen supply-demand that occurs during normothermic cardiopulmonary bypass and may represent transient cerebral ischemia. These episodes, however, are not associated with impared neuropsychological test performance as compared with the performance of patients with no evidence of desaturation.

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Cardiopulmonary bypass (CPB) is frequently complicated by postoperative neuropsychological dysfunction. Detectable decrements in cognitive function in the immediate postoperative period (5 to 8 days) have been noted by several investigators [1] in 11% to 75% of patients after CPB, with a median range between 24% and 34%. The neuropsychological dysfunction appears to be transient [2] and entirely consistent with a reversible diffuse ischemic insult [3]. Reversible cerebral ischemia may result from an imbalance between global oxygen supply and consumption, which, in turn, may be secondary to lowered cerebral perfusion during normothermic periods of CPB. The objective of this study was to determine the incidence of cerebral venous desaturation during a period of normothermic nonpulsatile CPB after hypothermic CPB in patients managed by alpha-stat control (temperature-uncorrected arterial carbon dioxide tension maintained at 40 mm Hg) of arterial blood gases. Furthermore, we assessed the relationship of desaturation to postoperative neuropsychological dysfunction. Jugular bulb venous oxygen tension ($PJvO_2$) and hemoglobin saturation ($SJvO_2$) were used as a reflection of cerebral oxygen consumption; preoperative and postoperative neuropsychological examinations were used to assess postoperative neuropsychological dysfunction.

Material and Methods

After institutional review board approval and written informed consent, 133 patients requiring CPB were entered into this study. Patients were premedicated with oral diazepam (0.1 mg/kg) and methadone hydrochloride (0.1 mg/kg) 90 minutes before induction of anesthesia. Catheters were placed in the radial artery and the right jugular bulb through the right internal jugular vein before induction of anesthesia for simultaneous sampling of systemic arterial and jugular venous blood at predetermined times. Anesthesia was induced and maintained with continuous infusion of midazolam hydrochloride and fentanyl citrate by computer-assisted continuous infusion [4]. Midazolam was infused to maintain a predicted blood level of 75 ng/mL and fentanyl, to maintain a predicted level of 6 ng/mL throughout the time of cerebral blood flow (CBF) measurements. Drug administration by computer-assisted continuous infusion has previously been shown to produce stable blood levels of anesthesia during CPB [5]. Vecuronium bromide was given as needed to maintain complete neuromuscular blockade.

The perfusion apparatus consisted of a Cobe CML oxygenator (Cobe Laboratories, Lakewood, CO) and a Sarns 7000 MDX pump (Sarns Inc, Ann Arbor, MI). Nonpulsatile perfusion of 2 L · min^{-1} · m^{-2} was maintained throughout the study periods. The pump was primed with crystalloid solution designed to achieve a hematocrit of 0.20 or higher during extracorporeal circu-

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lation. Packed red blood cells were added when necessary to achieve the desired hematocrit.

Extracranial 16-mm cadmium telluride detectors with wide-angle collimators were placed over the right and left temporal lobes, and the average of the values from both sites was used to determine CBF. Cerebral blood flow was calculated from data using zero modification of the initial slope method described by Olesen and associates [6]. The following formula was used:

$$\text{CBF } (\text{mL} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1}) = -\text{slope} \cdot \lambda \cdot 100$$

where slope is the slope of the natural logarithm of the count rate during the first minute of the xenon 133 (^{133}Xe) washout curve obtained by linear regression, and λ is the blood-brain partition coefficient corrected for temperature and hematocrit [7]. Baseline ^{133}Xe was measured before each measurement, and counts were subtracted from subsequent CBF values to correct for residual ^{133}Xe.

Xenon 133 (1.5 mCi dissolved in 3 mL of sterile saline solution) was administered into an injection port of the arterial perfusate circuit of the pump oxygenator. Arteriovenous oxygen content difference (C(a-v)O_2), cerebral metabolic rate for oxygen (CMRo_2), and oxygen delivery (Do_2) were calculated using the following equations:

$$\text{C(a-v)O}_2\ (\text{mL/dL}) = 1.39 \cdot \text{Hgb}(\text{SaO}_2 - \text{SJvO}_2) + 0.003(\text{PaO}_2 - \text{PJvO}_2)$$

$$\text{CMRo}_2\ (\text{mL} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1}) = [\text{CBF } (\text{mL} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1}) \cdot \text{C(a-v)O}_2\ (\text{mL/dL})]/100$$

$$\text{Do}_2\ (\text{mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}) = [\text{CaO}_2\ (\text{mL/100 mL}) \cdot \text{CBF } (\text{mL} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1})]/100$$

$$\text{O}_2 \text{ extraction} = \text{C(a-v)O}_2/[(1.39 \cdot \text{Hgb} \cdot \text{SaO}_2) + 0.0003 \cdot \text{PaO}_2] \cdot 100\%$$

where SaO_2 and SJvO_2 are arterial and venous oxygen saturation of the radial artery and jugular venous bulb blood, respectively, PaO_2 is arterial oxygen tension, CaO_2 is arterial oxygen content, and Hgb is hemoglobin concentration.

Cerebral blood flow and CMRo_2 determinations were made when the nasopharyngeal temperature reached 28°C and then at 36°C (after rewarming). Blood was drawn from the radial artery and jugular bulb catheters for determination of pH, oxygen tension, and oxygen saturation 1 minute after xenon injection. Blood gas values were determined with a BGE blood gas electrolyte analyzer (Instrumentation Laboratories, Lexington, MA). Oxygen saturation and hemoglobin measurements were made on an IL482 cooximeter (Instrumentation Laboratories). Arterial carbon dioxide tension was maintained throughout CPB at 35 to 40 mm Hg (uncorrected for body temperature) and PaO_2 at 150 to 250 mm Hg.

Neuropsychological testing was conducted preoperatively (baseline) and on day 7 postoperatively. The examiner was unaware of saturation status. The following tests were included in the assessment battery: digit symbol, digit span forward and backward, Randt short story, Benton visual retention, and trails B [1]. The digit symbol subtest of the Wechsler adult intelligence scale-revised is a paper-and-pencil task that requires subjects to reproduce, within 90 seconds, as many coded symbols as possible in blank boxes beneath randomly generated digits according to a coding scheme for pairing digits with symbols. The trail-making test (part B) requires subjects to connect, by drawing a line, a series of numbers and letters in sequence as quickly as possible. The short story module of the Randt memory test requires subjects to recall the details of a short story immediately after it has been read to them and then after a 30-minute delay. The digit span subtest of the Wechsler adult intelligence scale-revised requires subjects to repeat a series of digits that have been orally presented to them both forward and, in an independent test, in reverse order. The Benson revised visual retention test requires subjects to draw from memory a series of geometric shapes after a 10-second exposure.

Table 1. Demographic Variables[a]

Variable	Saturated Group (n = 102)	Desaturated Group (n = 31)
Age (y)	61.5 ± 11.5	62.1 ± 9.6
Sex (M/F)	62/40	25/6
Cross-clamp time (min)	53.1 ± 26.6	54.2 ± 23.1
CPB time (min)	116.6 ± 46.6	115.2 ± 31.3
Procedure		
CABG	63	22
Valve replacement or repair	32	8
CABG and valve procedure	7	1

[a] Where applicable, data are shown as the mean ± the standard deviation.

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; cross-clamp time = myocardial ischemic time.

Statistical Methods

All comparisons of continuous variables, such as age, between the saturated and desaturated groups were made using the nonparametric Wilcoxon rank sum test. For categorical variables such as sex, groups were compared with the Pearson χ^2 test. Statistical significance was defined as a p value of less than 0.05.

Results

One hundred thirty-three patients were entered into this study. Thirty-one (23%) met desaturation criteria ($\text{SJvO}_2 \leq 50\%$ or $\text{PJvO}_2 \leq 25$ mm Hg) during normothermic CPB (after hypothermic CPB at 27° to 28°C). The demographic data including age, sex, duration of cross-clamp time, duration of bypass, procedures, and anesthetic agents were not different between groups (Table 1). At normothermia, groups were similar with respect to nasopharyngeal temperature, SaO_2, PaO_2, hemoglobin level, and mean arterial pressure (Table 2). Cerebral blood flow was significantly higher in the saturated group (33.7 ± 10.3 mL · 100 g^{-1} · min^{-1}) than in the desaturated group (26.2 ± 6.9 mL · 100 g^{-1} · min^{-1}), whereas $CMRo_2$ was lower in the saturated group (1.28 ± 0.39 mL · 100 g^{-1} · min^{-1}) than in the desaturated group (1.52 ± 0.36 mL · 100 g^{-1} · min^{-1}) (see Table 2). Cerebral blood flow and $C(a\text{-}v)O_2$ during the two study periods are presented in Figure 1. The ratio of CBF to $C(a\text{-}v)O_2$ was significantly greater ($p < 0.0001$) in the saturated patients (see Table 2). The $C(a\text{-}v)O_2$ was greater in the desaturated group, a finding indicative of greater oxygen extraction. The desaturated group of patients also had lower oxygen delivery (2.67 ± 0.69 mL · 100 g^{-1} · min^{-1}) compared with the saturated group (3.45 ± 1.0 mL · 100 g^{-1} · min^{-1}) (Fig 2).

During hypothermic CPB, the group who experienced desaturation (criteria defined at normothermia) had a significantly lower $SJvO_2$ (68.8% ± 9.9%) compared with patients who remained saturated (76.7% ± 10.5%) (Table 3). The patients in the desaturated group also had a lower $PJvO_2$ (37.0 ± 7.7 mm Hg) compared with the saturated group (44.1 ± 11.1 mm Hg) (see Table 3). The $C(a\text{-}v)O_2$ was greater in the desaturated group (3.46 ± 1.16 mL/dL) than in the saturated group (2.61 ± 1.15 mL/dL). The oxygen extraction was also greater during hypothermic CPB in the group of patients who experienced desaturation compared with those who did not (33.4% ± 9.6% versus 25.5% ± 9.8%). Cerebral blood flow, $CMRo_2$, SaO_2, PaO_2, hemoglobin level, and mean arterial pressure were not significantly different between groups during hypothermic CPB (see Table 3). The ratio of CBF to $C(a\text{-}v)O_2$ during hypothermic CPB was lower in the desaturated group compared with the saturated group (7.31 ± 9.3 versus 10.2 ± 9.0).

Table 2. Physiological Variables at Normothermia[a]

Variable	Saturated Group (n = 102)	Desaturated Group (n = 31)
Temperature (°C)	36.5 ± 1.4	37.0 ± 0.7
CBF (mL · 100 g^{-1} · min^{-1})	33.7 ± 10.3	26.2 ± 6.9[b]
$CMRo_2$ (mL · 100 g^{-1} · min^{-1})	1.28 ± 0.39	1.52 ± 0.36[b]
SaO_2	0.98 ± 0.10	0.98 ± 0.09
$SJvO_2$	0.64 ± 0.09	0.44 ± 0.05[b]
PaO_2 (mm Hg)	215 ± 46.5	238 ± 53.7
$PJvO_2$ (mm Hg)	34.6 ± 6.1	24.7 ± 3.5[b]
CBF:$C(a\text{-}v)O_2$	9.8 ± 5.6	4.6 ± 1.6[b]
$C(a\text{-}v)O_2$ (mL/dL)	3.92 ± 1.12	5.97 ± 1.05[b]
Cerebral O_2 extraction	0.38 ± 0.09	0.57 ± 0.05[b]
Hemoglobin (g/dL)	7.2 ± 1.1	7.1 ± 1.1
MAP (mm Hg)	57.3 ± 8.8	55.0 ± 10.9
O_2 delivery (mL · 100 g^{-1} · min^{-1})	3.45 ± 1.0	2.67 ± 0.69[b]

[a] Data are shown as the mean ± the standard deviation. [b] Significance: $p < 0.005$.

$C(a\text{-}v)O_2$ = arteriovenous oxygen content deference; CBF = cerebral blood flow; $CMRo_2$ = cerebral metabolic rate of oxygen consumption; MAP = mean arterial pressure; PaO_2 = arterial oxygen tension; $PJvO_2$ = jugular bulb venous oxygen tension; SaO_2 = arterial oxygen saturation; $SJvO_2$ = jugular bulb oxygen saturation.

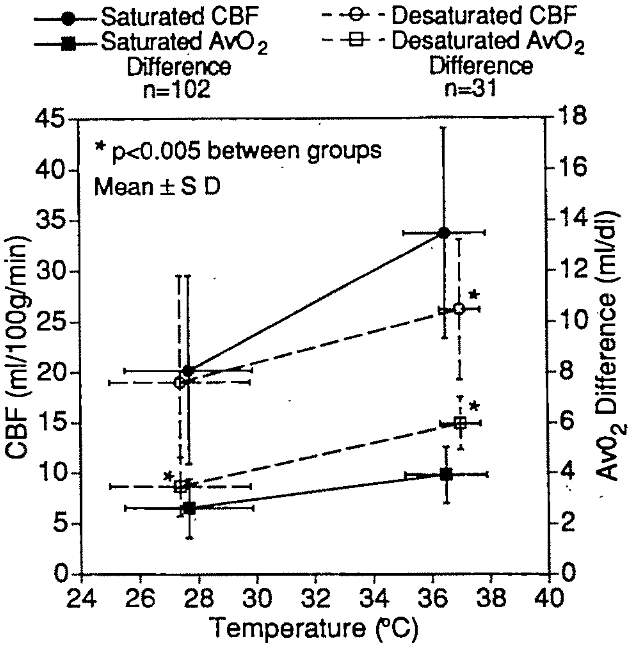

Fig 1. Effect of change in temperature on cerebral blood flow (CBF) and arteriovenous oxygen (AvO_2) difference in saturated and desaturated patients. With increasing temperature from 27.7° ± 2.4°C to 36.5° ± 1.4°C (saturated group) and from 27.4° ± 2.4°C to 37.0° ± 0.7°C (desaturated group), the change in CBF was significantly greater ($p < 0.002$) in the saturated patients (13.5 ± 10.5 mL · 100 g^{-1} · min^{-1} versus 7.3 ± 9.0 mL · 100 g^{-1} · min^{-1}). The change in AvO_2 difference was significantly greater ($p < 0.0001$) in the desaturated patients (2.51 ± 0.92 mL/dL versus 1.32 ± 1.16 mL/dL). (SD = standard deviation.)

During rewarming, CBF increased more in the saturated group (13.5 ± 10.5 mL · 100 g^{-1} · min^{-1}) than in the desaturated group (7.3 ± 9.0 mL · 100 g^{-1} · min^{-1}) (Table 4). Oxygen delivery increased to a greater extent in the saturated group. The change in $C(a\text{-}v)O_2$ was greater in the desaturated patients (2.51 ± 0.92 mL/dL) than in the saturated patients (1.32 ± 1.16 mL/dL).

Neuropsychological tests were performed in 74 patients: in 57 (55%) of the 102 patients who remained saturated and in 17 (55%) of the 31 patients who experienced desaturation. Mean scores on the tests revealed a decline in all of the tests performed postoperatively (Table 5). Trail-making test (part B) is a timed test; therefore, a positive change reflects a negative outcome. There was no difference between the two groups in the decline in test performance.

Comment

The present study demonstrates that 23% of the patients undergoing uneventful surgical intervention during extracorporeal circulation had significant jugular venous blood desaturation, defined as an $SJvO_2$ of less than or equal to 50% or a $PJvO_2$ of 25 mm Hg or less during the rewarming phase of nonpulsatile CPB. This marked desaturation of cerebral venous effluent was not associated with any

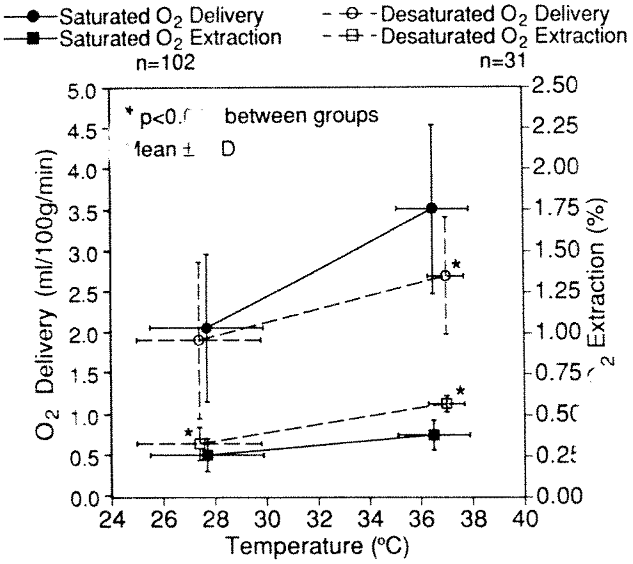

Fig 2. The effect of change in temperature on oxygen delivery and oxygen extraction. The change in oxygen delivery is 1.42 ± 1.10 mL · 100 g^{-1} · min^{-1} in the saturated patients and 0.77 ± 0.93 mL · 100 g^{-1} · min^{-1} in the desaturated patients < 0.002). Oxygen extraction increased from 0.26 ± 0.1 to 0.38 09 in the saturated patients and from 0.33 ± 0.1 to 0.57 ± 0.0[illegible] in the desaturated group. (SD = *standard deviation.)*

apparent exaggerated decline in postoperative neuropsychological dysfunction.

It is unclear whether these episodes of jugular venous desaturation represent cerebral ischemia, as the $SJvO_2$ or $PJvO_2$ below which brain ischemia occurs has yet to be established. Continuous monitoring of oxygen saturation in the venous blood of the lateral sinus during carotid endarterectomy in 50 patients revealed that cerebral dysfunction, defined as a transient neurological deficit, was observed in patients with saturations of less than 50%, and there were no cases of dysfunction with saturations of 60% or better [8]. In another study [9] of 20 patients having operation for cerebrovascular insufficiency, the investigators intervened to maintain $SJvO_2$ at greater than 60%. Using this strategy, there were no cases of overt central nervous system dysfunction. Electroencephalographic slowing regularly appeared when cerebral venous oxygen tension fell to less than 19 mm Hg ($SJvO_2$ < 40%) in 19 healthy volunteers monitored continuously with $PJvO_2$, $SJvO_2$ saturation, jugular venous bulb carbon dioxide tension, and pH [10]. Nelson [11] examined the effects of venous oxygen saturation in surgical patients and found that mixed venous hypoxia, defined as venous

Table 3. Physiological Variables at Hypothermia[a]

Variable	Saturated Group (n = 102)	Desaturated Group (n = 31)
Temperature (°C)	27.7 ± 2.19	27.4 ± 2.4
CBF (mL · 100 g^{-1} · min^{-1})	20.2 ± 9.3	19.0 ± 10.5
$CMRo_2$ (mL · 100 g^{-1} · min^{-1})	0.50 ± 0.23	0.59 ± 0.28
SaO_2	0.98 ± 0.01	0.98 ± 0.09
$SJvO_2$	76.7 ± 10.5	68.8 ± 9.9[b]
PaO_2 (mm Hg)	216 ± 46.0	227 ± 42.4
$PJvO_2$ (mm Hg)	44.1 ± 11.1	37.0 ± 7.7[b]
$C(a\text{-}v)O_2$ (mL/dL)	2.61 ± 1.15	3.46 ± 1.16[b]
$CBF:C(a\text{-}v)O_2$	10.2 ± 9.0	7.31 ± 9.3[c]
Cerebral O_2 extraction	0.26 ± 0.1	0.33 ± 0.1[b]
Hemoglobin (g/dL)	7.0 ± 1.3	7.1 ± 1.0
MAP (mm Hg)	58.2 ± 11.5	62.2 ± 12.4
O_2 delivery (mL · 100 g^{-1} · min^{-1})	2.03 ± 0.89	1.89 ± 0.95

[a] Data are shown as the mean ± the standard deviation. [b] Significance: $p < 0.005$. [c] Significance: $p < 0.05$.

Abbreviations are the same as in Table 2.

Table 4. Changes in Physiological Variables During Rewarming

Variable	Saturated Group (n = 102)	Desaturated Group (n = 31)	p Value
ΔCBF (mL · 100 g^{-1} · min^{-1})	13.5 ± 10.5	7.3 ± 9.0	<0.002
$\Delta CMRo_2$ (mL · 100 g^{-1} · min^{-1})	0.78 ± 0.35	0.93 ± 0.32	NS
$\Delta C(a\text{-}v)O_2$ (mL/dL)	1.32 ± 1.16	2.51 ± 0.92	<0.0001
$\Delta CBF:C(a\text{-}v)O_2$	−0.29 ± 8.40	−2.79 ± 9.04	<0.02
ΔO_2 delivery (mL · 100 g^{-1} · min^{-1})	1.42 ± 1.10	0.77 ± 0.93	<0.002

Δ = change in variable between hypothermia and normothermia; NS = not significant; other abbreviations are the same as in Table 2.

Table 5. Neuropsychological Variables[a]

Test	Group	No. of Patients	Change (preop to postop)	p Value[b]
Digit symbol	Saturated	56	−4.1 ± 6.9	<0.005
	Desaturated	17	−6.2 ± 7.2	<0.005
Randt short story intermediate verbatim	Saturated	57	−0.05 ± 2.9	
	Desaturated	17	−0.35 ± 2.7	
Benton visual retention	Saturated	51	−1.00 ± 2.0	<0.005
	Desaturated	17	−1.18 ± 2.8	
Trail-making test (part B)	Saturated	51	3.29 ± 57.5	
	Desaturated	15	3.07 ± 34.6	
Digit span forward	Saturated	56	−0.20 ± 1.6	
	Desaturated	17	−0.82 ± 1.6	<0.05
Digit span backward	Saturated	55	−0.75 ± 1.9	<0.05
	Desaturated	17	−1.24 ± 1.2	<0.005
Randt delayed verbatim	Saturated	55	−0.97 ± 3.2	<0.05
	Desaturated	17	−0.29 ± 3.2	

[a] Data are shown as the mean ± the standard deviation. [b] Significance is for the change in test scores from preoperatively to postoperatively.

oxygen tension lower than 27 mm Hg and venous oxygen saturation lower than 50%, lead to lactic acidosis in most patients. Based on these clinical observations, jugular bulb venous oxygen desaturation was defined as $PJvO_2$ of 25 mm Hg or less or $SJvO_2$ of 50% or less in the present study.

We recognize that no previous study has defined a critical level of jugular venous bulb desaturation during normothermic CPB. During CPB, temperature is the main determinant of cerebral oxygen consumption, and CBF and hemoglobin levels are the main determinants of cerebral oxygen delivery. A 1983 study [12] involving 58 anesthetized patients before CPB observed that when total-body oxygen delivery was less than 330 mL $\cdot$ min^{-1} $\cdot$ m^{-2}, mixed venous oxygen tension decreased in proportion to the decrease in delivery, suggesting a compensatory increase in oxygen extraction, whereas total-body oxygen consumption decreased in proportion to delivery, implying tissue oxygen deprivation occurred. Using mixed venous oximetry, Baraka and co-workers [13] demonstrated that alterations in extracorporeal pump flow at hypothermia did not result in significant mixed venous desaturation (defined as venous oxygen saturation $< 70\%$). However, desaturation occurred with alterations in pump flow at normothermia (37°C) [13], implying greater dependency of oxygen delivery on extracorporeal pump flow during normothermia.

Although direct comparison with the present study is problematic, many of the principles of total-body oxygen delivery can be applied to cerebral oxygen delivery. Thus, during (and after) rewarming from hypothermic CPB, cerebral oxygen requirements may exceed cerebral oxygen delivery. There are several possible causes of this problem: loss of cerebral autoregulation, alterations in blood flow because of nonpulsatile CPB, moderate hemodilution, or other factors, alone or in combination.

A discussion of the determinants of CBF and cerebral oxygen consumption during CPB is particularly germane to the conclusions of this study. Cerebral blood flow in healthy humans is directly related to arterial carbon dioxide tension, temperature, and cerebral metabolism [14, 15]. The coupling of CBF to $CMRo_2$ (metabolic autoregulation) and the maintenance of a constant CBF during arterial perfusion pressure fluctuation (pressure–flow autoregulation) are preserved during CPB if alpha-stat blood gas management is employed [14–16], as in the present investigation. Metabolic autoregulation has been demonstrated to be intact in the elderly [17] and the very young [18]; however, cerebral autoregulation is impaired in diabetic patients [19] and during profound hypothermia [20]. In these investigations, a calculated cerebral oxygen consumption ($CMRo_2$) was coupled to CBF; $C(a-v)O_2$ was examined in detail only in diabetic patients and during profound hypothermia. Arteriovenous oxygen content difference, which is independent of CBF, may be a more sensitive measure of cerebral oxygen balance, but the critical level of cerebral $C(a-v)O_2$ has yet to be established during nonpulsatile CPB.

Metabolic uncoupling has been suggested as a mechanism of intracellular hypoxia occurring during profound hypothermic CPB in children [21]. This preliminary report found cerebral cytochrome *aa*$_3$ oxidation was decreased after low-flow, profoundly hypothermic CBP in the absence of changes in $CMRo_2$. Although similar methodologies were used in that study of pediatric patients and in our present study, extrapolation of these results and postulated mechanisms to the present study is problematic, in part because of differences in patient population (adult versus pediatric), conduct of CPB, lack of cytochrome *aa*$_3$ measurements in the present study, and lack of CBF measurements in the study of Bracey and colleagues [21]. The desaturation observed in the present study may be a result of inadequate CBF in proportion to consumption, as indicated by an increased $C(a-v)O_2$. The group of patients who subsequently experienced significant jugular venous bulb desaturation during rewarming had lower $PJvO_2$ and $SJvO_2$ values during the hypothermic CPB phase compared with the group of patients who maintained jugular venous bulb saturation during the rewarming phase (see Tables 2, 3). There was no such difference in PaO_2 and SaO_2 between groups; therefore, the $C(a-v)O_2$ and oxygen extraction during hypothermia were greater in patients who eventually experienced significant desaturation at normothermia (see Tables 2, 3).

There was no significant difference in CBF or oxygen delivery between groups at hypothermia. However, the ratio of CBF to $C(a-v)O_2$ was lower during hypothermia in the patients who had desaturation compared with the group who did not (see Table 3). More importantly, there was a significantly greater change in the CBF to $C(a-v)O_2$ ratio from hypothermic CPB to normothermic CPB in the patients who experienced desaturation. The lower ratio during hypothermia reflects impairment of CBF responsiveness to metabolic demand that is further compromised during the metabolic stress of rewarming in these patients. Indeed, CBF was significantly lower in the group of patients with desaturation during the rewarming phase. As might be expected, the CBF to $C(a-v)O_2$ ratio was significantly lower in the desaturated group than in the saturated group after rewarming, a finding possibly indicative of increased metabolic demand, impaired metabolic autoregulation, or a combination of the two. Patients with desaturation have either a primary increase in metabolic demand because of unknown cerebral mechanisms during the warming phase or a CBF inadequate to meet normothermic cerebral metabolism. Thus, normothermic jugular venous bulb oxygen desaturation reflects some defect in metabolic autoregulation.

Declines in cognitive performance were observed in the majority of tests that we employed. These declines were comparable for both the saturated and desaturated groups and indicated reduced performance on tasks generally considered to reflect measures of attention, concentration, and psychomotor speed. Presumably the desaturation that we found is compatible with adequate cerebral oxygenation, although the neuropsychological testing data were not available on all patients, and this conclusion is based on a relatively small sample size. Although neuropsychological test scores were reduced in both groups of patients, the magnitude of the effect was relatively small and may reflect only subclinical changes in cognitive function. The clinical significance of these changes is not known, and the duration of cognitive dysfunction has been found to be relatively brief [22, 23].

It is important to emphasize that the relationships among metabolism, flow, and pressure have not been studied with dynamic monitors. Our measurements of CBF and CMRo$_2$ were made at steady state and represent static data points. Thus, the duration of the episode of desaturation and the rate at which the saturation fell could not be determined in the present study. Introduction of continuous monitors of CBF and CMRo$_2$ may further describe this phenomenon. This information would permit better characterization of desaturation and its relationship to postoperative central nervous system function. Jugular venous bulb oxygen saturation is an expression of considerable clinical value because it is a measure of the ability of blood flow to meet metabolic demands. Based on our observations, an SJvO$_2$ of less than 50% is encountered in 23% of patients but does not necessarily lead to cognitive dysfunction. This degree of desaturation probably reflects the capacity of the brain to extract when it is not adequately supplied.

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Cytokine Responses to Cardiopulmonary Bypass With Membrane and Bubble Oxygenation

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The systemic inflammatory response to cardiopulmonary bypass was assessed in 20 patients who underwent elective coronary artery bypass grafting with flat-sheet membrane oxygenation (group I; n = 10; age, 59 ± 5 years) or bubble oxygenation (group II; n = 10; age, 62 ± 8 years). The duration of cardiopulmonary bypass was 46 ± 12 minutes in group I and 47 ± 15 minutes in group II. Plasma interleukin-6, plasma interleukin-1β, transpulmonary leukocyte counts, pulmonary hemodynamic variables, and respiratory index were determined in all patients perioperatively. The plasma interleukin-6 response (median [range]) was similar in both groups at the end of the operation, peaked 4 hours postoperatively (99 [30 to 320] pg/mL in group I; 123 [21 to 300] pg/mL in group II; $p > 0.05$), and remained elevated 48 hours postoperatively (76 [9 to 140] pg/mL in group I; 65 [25 to 159] pg/mL in group II; $p > 0.05$). No significant interleukin-1β response was demonstrated. Pulmonary neutrophil and lymphocyte sequestration was observed on commencement of cardiopulmonary bypass in group II but did not occur in either group on discontinuation of cardiopulmonary bypass. Pulmonary vascular resistance at the end of the operation (82 [48 to 320] dynes · s · cm^{-5} in group I; 119 [54 to 385] dynes · s · cm^{-5} in group II; $p > 0.05$) was similar to preoperative values (151 [30 to 327] dynes · s · cm^{-5} in group I; 185 [62 to 291] dynes · s · cm^{-5} in group II; $p > 0.05$). The respiratory index at the end of the operation was similarly and significantly increased in both groups (1.26 [0.92 to 4.17] in group I; 1.44 [0.73 to 3.30] in group II). Cardiopulmonary bypass with both membrane and bubble oxygenation was followed by a significant interleukin-6 response; pulmonary neutrophil sequestration did not occur after cardiopulmonary bypass, although significant impairment of oxygenation was still found after perfusion of short duration.

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Cardiopulmonary bypass (CPB) induces systemic inflammatory responses that have been implicated in postoperative organ dysfunction [1]. The role of cytokines in these responses has not yet been established. Interleukin-6 (IL-6) is produced by many cell types [2] and may be the main inducer of the acute-phase response to injury [3]. Interleukin-6 induces acute phase proteins in vitro [4] and in vivo [5] and has been detected in serum after burn injury [6] and elective operation [7]. Levels may be of prognostic value in septic shock [8]. Interleukin-1β (IL-1) is produced predominantly by monocytes [9] and endothelial cells [10] in response to endotoxin [11] and complement anaphylatoxins [12]. It plays an important role in acute inflammation and microvascular injury [11]. Interleukin-1β has important systemic effects including hypotension [13] and fever [14]; it induces human neutrophil degranulation [15] and induces IL-6 synthesis by monocytes [16].

Complement activation occurs during CPB [17, 18], and binding of C5a to a specific receptor on the neutrophil membrane [19] may stimulate neutrophil adherence to pulmonary endothelium [20] with intrapulmonary neutrophil sequestration at the time of lung reperfusion [17]. Neutrophil degranulation and free radical release may lead to endothelial and epithelial injury [21, 22], indirectly detected by an increase in lipid peroxidation products in plasma [23].

Comparative studies of the degree of complement activation and organ dysfunction with membrane and bubble oxygenation have been inconclusive [24–27]. In one study, an increase in pulmonary vascular resistance and extravascular lung water occurred only after bubble oxygenation [28], suggesting a greater degree of lung injury with this type of oxygenator.

In this pilot study IL-6, IL-1, and leukocyte responses to CPB with both membrane and bubble oxygenation were assessed to determine their role in postoperative pulmonary dysfunction.

Material and Methods

Twenty patients undergoing elective coronary artery bypass grafting for ischemic heart disease were studied. Either a membrane oxygenator (Cobe CML [Cobe Laboratories, Ltd, Gloucester, UK], group I, n = 10) or bubble oxygenator (William Harvey H-1700 [Bard Ltd, Crawley, UK], group II, n = 10) was randomly assigned for use in the extracorporeal circuit. The two groups were well

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Table 1. Preoperative Data[a]

Variable	Group I	Group II	*p* Value[b]
Age (y)	59 ± 5	62 ± 8	NS
Sex (M:F)	9:1	9:1	NS[c]
RFTs (% predicted)			
FEV_1	84 ± 10	86 ± 14	NS
FVC	94 ± 14	89 ± 13	NS
PEF	75 ± 16	84 ± 28	NS
NYHA class			NS[c]
II	6	3	
III	4	7	
CPB (min)	46 ± 12	47 ± 15	NS[c]
Grafts (No.)			NS[c]
2	5	4	
3	4	5	
4	1	1	

[a] Data are shown as the mean ± the standard deviation. [b] By unpaired *t* test unless otherwise indicated. [c] By χ^2 test.

CPB = duration of cardiopulmonary bypass; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; group I = membrane oxygenation; group II = bubble oxygenation; PEF = peak expiratory flow; NYHA = New York Heart Association anginal class; RFTs = respiratory function tests (preoperative).

matched in terms of age, sex, and preoperative respiratory function (Table 1).

Regular medications were continued up to the morning of operation. Premedication was by papaveretum (10 to 20 mg) and scopolamine (0.4 mg) intramuscularly 1 hour before operation. No corticosteroids were administered before or during the operation. Anesthetic induction and maintenance and neuromuscular blockade were achieved with fentanyl (10 to 15 μg/kg), thiopentone (1 to 2 mg/kg), pancuronium bromide (0.1 to 0.15 mg/kg), oxygen with nitrous oxide (50%), and halothane (0.5 to 1.0%). An infusion of nitroglycerin was titrated for blood pressure control.

The extracorporeal circuit consisted of a roller pump, a two-stage right atrial cannula or basket for venous drainage, a cardiotomy reservoir (Sorin Biomedica, Midhurst, UK), a membrane or bubble oxygenator, and arterial line filter (Pall Biomedical Ltd, Portsmouth, UK) with arterial return to the ascending aorta. The circuit was primed with 2 to 2.5 L of Ringer's lactate. Heparin (3 mg/kg body weight) was infused to maintain an activated clotting time of more than 400 seconds during bypass. Flow rates of 2.4 $L \cdot m^2 \cdot min^{-1}$ were used, maintaining a systemic perfusion pressure of 40 to 60 mm Hg. Two different techniques of myocardial preservation were used: either intermittent aortic cross-clamping with a fibrillating heart and a core temperature of 33° to 34°C (n = 5 in each group) or cold cardioplegia supplemented by ice/slush topical hypothermia and a core temperature of 30° to 32°C (n = 5 in each group). Cardiopulmonary bypass was terminated at a core temperature of 36.8° to 37°C with the patient in sinus rhythm. On discontinuation of bypass, anticoagulation was reversed by protamine sulfate (1 mg/kg body weight). Cardiopulmonary bypass times and the number of coronary grafts were similar in the two groups (see Table 1). Inotropic support was not required in the postoperative period. During recovery, morphine (1 to 2 mg/h) for analgesia and nitroglycerin titrated for blood pressure control were infused.

Serial simultaneous blood samples were taken from the pulmonary and radial artery catheters for differential leukocyte counts (A) before induction of anesthesia, (B) after induction, before sternotomy; (C) after heparin administration, before CPB; (D) 1 minute on CPB with the heart still ejecting (arterial sample taken from the left atrium); (E) 20 minutes on CPB; (F) 5 minutes before final cross-clamp removal; (G) 5 minutes after final cross-clamp removal; (H) at the end of CPB; (I) after protamine infusion; (J) after sternal closure; (K) 2 hours postoperatively; (L) 4 hours postoperatively; (M) 6 hours postoperatively; (N) 24 hours postoperatively; and (P) 48 hours postoperatively. Differential leukocyte counts were performed by a H-6000 Coulter counter on blood anticoagulated with ethylenediaminetetraacetic acid (EDTA). Blood (4 mL, anticoagulated with EDTA to a final concentration of 3.4 mmol/L) collected at (B), (E), (J), (K), (L), (M), (N), and (P) was centrifuged (1,500 *g* for 10 minutes) at 4°C, and plasma was stored at −70°C until assayed. Results were not corrected for hemodilution. Thermodilution cardiac outputs (mean of three readings) were determined using a Sieman computer at (B), (J), and (K) and the systemic and pulmonary vascular resistances were then computed using standard formulae.

The respiratory index (RI) (calculated from the alveolar-arterial oxygen gradient to partial pressure of arterial oxygen ratio) was used as a measure of oxygenation because it reflects intrapulmonary shunting while being independent of the fraction of inspired oxygen [29]. The inspired oxygen fraction was determined by an Oxychec monitor (Tampa, FL), and the oxygen tension in peripheral blood by analysis of a heparinized sample on a 1306 Blood Gas Analyzer (Instrumentation Laboratory, Milan, Italy) at (B), (J), (K), (L), and (M). The levels of IL-1 (Medgenix Diagnostics, intraassay and interassay variation, 2.8% and 4.5%, respectively) and IL-6 (British Biotechnology Ltd, intraassay and interassay variation, 8.1% and 7.5%, respectively) were determined in duplicate by enzyme-linked immunosorbent assay using established kits.

The significance of differences was assessed by paired or unpaired *t* tests for normally distributed data or by Wilcoxon signed-rank tests (paired data) and Mann-Whitney U tests as appropriate. Peak values or the area under the response curve (sum of the product of time differences and means of two consecutive readings) were used in the analysis of multiple repeated measures [30]. Association between two numeric variables was assessed by Spearman's rank correlation. Significance was accepted where *p* was less than 0.05. Results in the text and tables are expressed as mean ± standard deviation or median and range as appropriate.

Informed verbal consent was obtained for the study, which had local ethical committee approval.

Results

Plasma IL-6 was detectable preoperatively in 4 group I patients and 6 group II patients (Table 2). In both groups, plasma levels were significantly elevated above baseline at the end of operation ($p < 0.01$) and peaked 4 hours postoperatively, remaining significantly above baseline 48 hours postoperatively ($p < 0.01$). Peak levels of IL-6 and the area under the response curves were similar in both groups. There was no relation between peak IL-6 levels and the duration of CPB.

Interleukin-1β was not detectable preoperatively in group I but was in 2 group II patients (data not shown). No IL-1 response to CPB was observed.

Pulmonary neutrophil and lymphocyte sequestration, assessed by total transpulmonary counts, occurred in group II after 1 minute of CPB. An increased but nonsignificant venoarterial gradient also occurred in group I at this time ($p > 0.05$). Sequestration was observed in neither group at the time of lung reperfusion after cardiopulmonary bypass (Figs 1, 2).

The pulmonary vascular resistance was lower postoperatively in both groups when compared with preoperative values, although within-group and between-group differences were not statistically significant (Table 3). In group I, there was a significant fall in the systemic vascular resistance and a significant increase in the cardiac index postoperatively.

The RI was increased at the end of the operation in both groups ($p < 0.01$), improving gradually over the following 4 hours (Table 4). The RI peak and area under the response curve from 0 to 6 hours postoperatively was similar in both groups. The preoperative RI correlated with the peak postoperative RI value in group I ($r_S = 0.69$; $p < 0.05$) but not in group II. There was no correlation between the postoperative RI and preoperative respiratory function tests, CPB time, or IL-6 levels.

Table 2. Perioperative Plasma Interleukin-6 Levels

	Interleukin-6 (pg/mL)			
	Group I		Group II	
Time	Median	Range	Median	Range
(B) After induction	0	0–36	7	0–24
(E) 20 min bypass	0	0–44	11	8–15
(J) Sternal closure	32	7–90	29	13–36
(K) 2 h postoperative	81	18–190	97	33–160
(L) 4 h postoperative	99	30–320	123	21–300
(M) 6 h postoperative	83	25–280	108	35–310
(N) 24 h postoperative	77	8–150	80	15–250
(P) 48 h postoperative	76	9–140	65	25–159

Group I = membrane oxygenation; group II = bubble oxygenation.

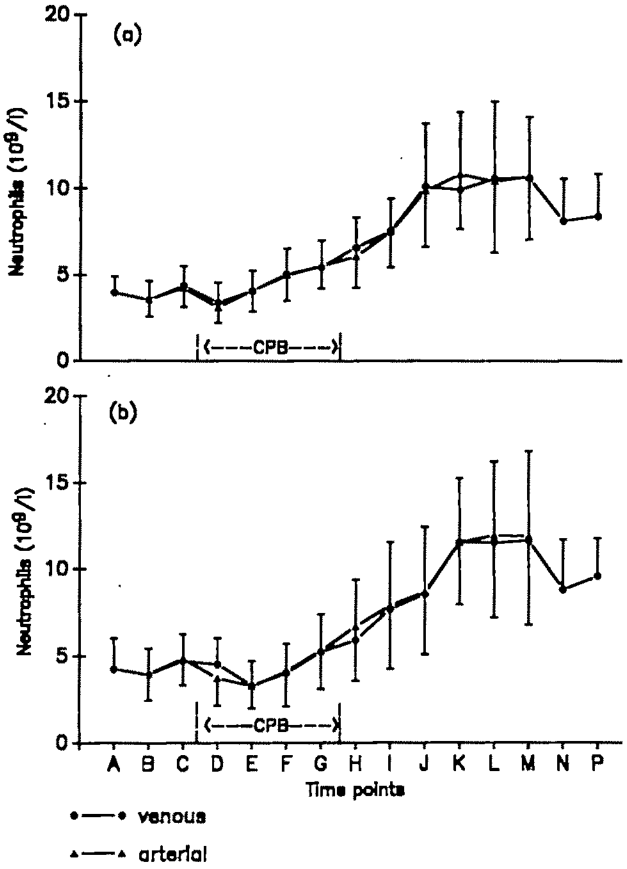

Fig 1. Perioperative mixed venous and arterial neutrophil counts in (a) membrane and (b) bubble oxygenator groups. (CPB = cardiopulmonary bypass; see text for time points.)

Comment

This study demonstrated a strong IL-6 response to CP with both membrane and bubble oxygenation. No intra pulmonary leukocyte sequestration occurred on discon tinuation of CPB. Hemodynamic variables and postoper ative oxygenation followed a similar pattern in bot groups.

The pattern of the IL-6 response is consistent with it role as a major mediator of the acute-phase response t injury. This response is characterized by fever, leukocy tosis, a negative nitrogen balance, increased vascula permeability, and an increase in the synthesis of hepati acute-phase proteins [31]—changes seen after cardiopul monary bypass. C-reactive protein peaks about 46 hour after a cardiac operation [32], and peak IL-6 and peal C-reactive protein levels correlate significantly after gen eral operations [33]. The level of IL-6 increases earlier tha that of acute-phase proteins and is related to the genera tion of fever after a burn injury [6]. Interleukin-6 coul therefore be an important mediator of the systemic re sponses to CPB, and because levels after cholecystectom have been correlated with the duration of operation [7], i may be a useful marker of the severity of tissue injury. I our study, peak levels did not correlate with the duratio of CPB, but the groups were homogeneous and the rang of CPB times was narrow.

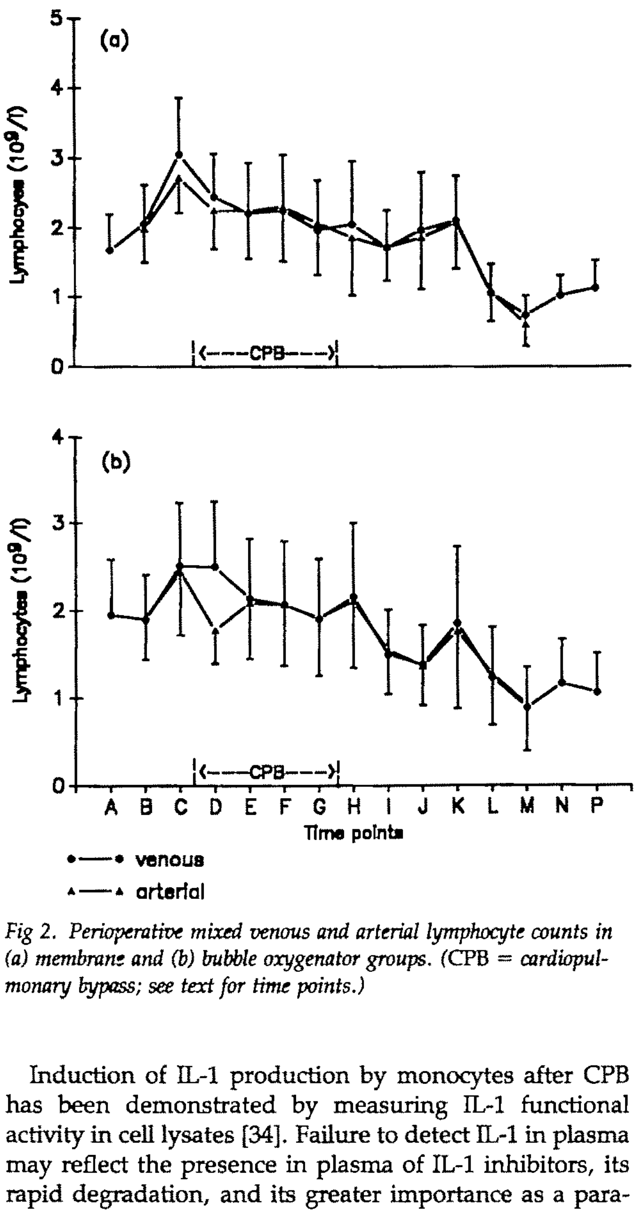

Fig 2. Perioperative mixed venous and arterial lymphocyte counts in (a) membrane and (b) bubble oxygenator groups. (CPB = cardiopulmonary bypass; see text for time points.)

Table 4. Perioperative Respiratory Index

	Group I		Group II	
Time	Median	Range	Median	Range
(B) After induction	0.60	0.03–1.06	0.69	0.28–1.32
(J) Sternal closure	1.26	0.92–4.17	1.44	0.73–3.30
(K) 2 h postoperative	1.19	0.62–2.46	1.45	0.20–3.75
(L) 4 h postoperative	0.95	0.29–2.96	1.34	0.57–4.19
(M) 6 h postoperative	1.11	0.35–1.91	1.60	0.45–3.97

Group I = membrane oxygenation; group II = bubble oxygenation.

Induction of IL-1 production by monocytes after CPB has been demonstrated by measuring IL-1 functional activity in cell lysates [34]. Failure to detect IL-1 in plasma may reflect the presence in plasma of IL-1 inhibitors, its rapid degradation, and its greater importance as a paracrine mediator. Circulating IL-1 was detected in only 4 of 18 patients with meningococcal sepsis [35], and it could not be detected after intravenous endotoxin administration [36].

Neutrophil and lymphocyte sequestration at the commencement of CPB has been previously noted [37]. This may be a physiological response as the number of intrapulmonary neutrophils is inversely related to the pulmonary blood flow [38]. We found no evidence of a transpulmonary gradient in total or differential leukocyte counts on discontinuation of CPB, either because it did not occur or because we failed to detect it. Lesser degrees of sequestration, not detectable by simultaneous sampling from the pulmonary and radial artery catheters, cannot be ruled out. Samples were not taken from the left atrium after aortic cross-clamp removal [23, 37] because full CPB is maintained at this time and pulmonary blood flow is minimal. Left atrial leukocyte counts may therefore lag behind the rapidly rising mixed venous counts and lead to false evidence of sequestration. With the techniques used in this study, discontinuation of CPB was rapid and a period of partial perfusion unnecessary, again differing from the methods used to demonstrate sequestration in other studies [17]. The sequestration previously demonstrated immediately after CPB [24, 39] was not observed, supporting a report of transient sequestration in only 2 of 10 patients at this time [40]. The duration of CPB in our study was considerably shorter than those in previous reports and may be a possible explanation for the failure to detect sequestration. Significant correlations between the extent of pulmonary vascular leukosequestration, the duration of aortic cross-clamping, and the duration of CPB have been demonstrated [17], and pulmonary histological changes increased with extended CPB, particularly when in excess of 150 minutes [41, 42]. Severe damage to endothelial and membranous pneumocytes was demonstrated only in the presence of large numbers of neutrophils.

No significant difference between membrane and bub-

Table 3. Cardiac Index and Systemic and Pulmonary Vascular Resistances

	CI (L · m² · min⁻¹)				SVR (dynes · s · cm⁻⁵)				PVR (dynes · s · cm⁻⁵)			
	Group I		Group II		Group I		Group II		Group I		Group II	
Time	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
(B)	2.2	1.3–2.7	1.8	1.4–3.3	1,657	1,088–2,947	1,470	738–2,488	151	30–327	185	62–291
(J)	2.9	2.1–4.7	2.2	1.3–3.2	1,279	780–1,620	1,201	787–1,837	82	48–320	119	54–385
(K)	3.0	1.9–4.1	1.8	1.1–5.1	982	569–1,640	1,734	408–3,320	74	15–160	193	67–523

(B) = after induction; CI = cardiac index; group I = membrane oxygenation; group II = bubble oxygenation; (J) = sternal closure; (K) = 2 hours postoperative; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

ble oxygenation was found in the inflammatory responses assessed in this pilot study. We found a nonsignificant reduction in pulmonary vascular resistance postoperatively when compared with preoperative values. As this occurred in both the bubble and membrane oxygenator groups, we cannot support the finding of Byrick and Noble [28], who demonstrated a rise in PVR only after bubble oxygenation. They postulated that this rise was a consequence of increased hemolysis and blood element destruction, denaturation of proteins, and the presence of circulating microbubbles. Such factors may be important after prolonged perfusion [43].

The increase in RI postoperatively was not significantly different between the two groups. The correlation between the preoperative and postoperative values of RI in the membrane oxygenator group indicates that preoperative pulmonary function is the most important determinant of postoperative oxygenation.

This study demonstrated elevated IL-6 levels after CPB with both membrane and bubble oxygenators, which may be of importance in the systemic responses to CPB. Post-cardiopulmonary bypass intrapulmonary neutrophil sequestration and therefore acute lung injury may not be a significant problem after short-term bypass. Further studies are required to determine the relative contribution of operation and CPB to the IL-6 response in perfusion of both short and long durations.

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Leukocyte Activation With Increased Expression of CR3 Receptors During Cardiopulmonary Bypass

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The effects of cardiopulmonary bypass (CPB) on the expression of leukocyte adhesive receptors, ie, complement receptor type 3 (CR3), were studied in 16 patients. The CR3 expression on leukocytes was determined by time-resolved fluoroimmunoassay on a standardized number of cells isolated from blood samples taken during various times during CPB. The results demonstrated that CR3 expression on leukocytes increased immediately after the start of CPB ($p < 0.05$), concomitant with an early sharp increase of plasma concentrations of C3a ($p < 0.01$). After release of the aortic cross-clamp, a second peak of leukocyte CR3 expression was induced ($p < 0.05$), paralleled by a significant increase of leukotriene B_4 ($p < 0.05$) and elastase ($p < 0.05$) levels in the late period of CPB. In vitro studies with leukocytes isolated from healthy donors ($n = 5$) showed a dose-dependent increase of CR3 expression stimulated by zymosan-activated plasma, indicating that the rapid CR3 expression on leukocytes is likely mediated by complement activation. However, the mechanisms for the second peak of leukocyte CR3 expression during CPB remain to be further elucidated. In conclusion, CR3 expression on leukocytes increased immediately after the start of CPB and was followed by a second peak of expression in the late phase of CPB. Pharmacological blockage of these adhesive receptors might reduce the leukocyte-mediated deleterious effects of CPB.

(Ann Thorac Surg 1992;53:839–43)

Postoperative morbidity after cardiac operations has been related to the damaging effects of cardiopulmonary bypass (CPB) [1–3]. These damaging effects are considered to be mediated mainly by the activation of leukocytes as a result of complement activation initiated by blood–material interaction [4–6]. Previous studies [7] demonstrated that anaphylatoxins such as C5a generated during complement activation promote leukocyte activation through C5a receptors on the cell surface of polymorphonuclear leukocytes (PMNs). However, next to activation by C5a, PMN adhesion to the target is required to initiate their local effect and mediate endothelial cell damage [8, 9]. Thus, expression of adhesive receptors, ie, complement receptor type 3 (CR3), on the PMN surface must be anticipated as a prerequisite for the local release of inflammatory mediators by leukocytes during CPB.

We performed a study involving 16 patients having coronary artery bypass grafting to investigate the effect of CPB on the membrane expression of CR3 on leukocytes as well as other variables indicating complement and leukocyte activation during CPB. In addition, we performed in vitro studies on isolated leukocytes obtained from healthy donors and stimulated with zymosan-activated plasma to assess whether the increased CR3 expression on leukocytes was dependent on the increased activation of complement.

Material and Methods

Sixteen patients undergoing CPB for selective coronary artery bypass grafting were prospectively scheduled for this study. None of the patients had preoperative signs of infection. Informed consent was obtained from each of the patients the day before operation, and the study was approved by the ethical committee of the hospital.

After premedication with diazepam (10 to 15 mg), anesthesia was induced by sufentanil citrate (3 to 5 μg/kg), and muscle relaxation was achieved with pancuronium bromide (100 to 140 μg/kg). Analgesia was provided by sufentanil and midazolam hydrochloride infusion. Cefamandole nafate, 2 g, and dexamethasone, 1 mg/kg, were administered preoperatively. Anticoagulation was achieved by intravenous administration of bovine lung heparin sodium (300 IU/kg).

Cardiopulmonary Bypass

The extracorporeal circuit consisted of roller pumps and either a hollow-fiber membrane oxygenator (BOS-CM50; Bentley/Baxter Inc, Irvine, CA) or a microporous polypropylene membrane oxygenator (CML EXCEL; COBE Laboratories, Inc, Lakewood, CO). The circuit was primed with a gelatin containing crystalloid solution (Gelifundol; Biotest Pharma GmbH, Dreieich, Germany) and 1,500 IU of heparin.

After institution of CPB, the aorta was cross-clamped, and 1 L of St. Thomas' cardioplegic solution (4°C) was infused into the aortic root to provide myocardial preservation. At the same time, moderate hypothermia was induced to maintain the nasopharyngeal temperature

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between 26° and 28°C. The mean arterial pressure was kept between 50 and 60 mm Hg during bypass. After completion of all the distal anastomoses, the aortic cross-clamp was removed, and the proximal anastomoses were performed while the patient was being rewarmed to 37°C. After CPB, heparin was neutralized by slow infusion of protamine hydrochloride (3 mg/kg) through the right atrium. The mean duration of CPB was 109.6 ± 8.3 minutes.

Measurements

Blood samples were taken after heparinization but before CPB, at 5 minutes and 30 minutes after the initiation of CPB, 5 minutes before and after release of the aortic cross-clamp, and at the end of CPB from the indwelling radial artery catheter. Circulating leukocyte count and sample hematocrit were measured by a cell counter (Cell-Dyn 610; Sequoia-Turner, Mountain View, CA). Samples for determination of leukocyte CR3 expression and measurement of leukocyte release products were mixed with 3.06% sodium citrate, whereas samples for measurement of complement were anticoagulated with EDTA (ethylenediaminetetraacetic acid). Plasma was obtained by centrifugation of whole blood at 1,000 *g* and stored at −20°C for further studies.

LEUKOCYTE ISOLATION. Leukocytes were isolated by combined sedimentation and hypotonic lysis technique according to the method described previously [10]. The harvested leukocytes were resuspended in phosphate-buffered saline solution containing a leukocyte concentration of 4.0 × 10^9/L including approximately 70% PMNs.

LEUKOCYTE CR3 RECEPTORS. Expression of CR3 on the isolated leukocytes was determined by time-resolved fluoroimmunoassay [11]. Monoclonal antibodies against human CR3 (Dakopatts a/s, Glostrup, Denmark) were labeled with europium 3^+, and this labeled antibody solution (containing 4.7 nmol/mL immunoglobulin G) was incubated with 4 × 10^6/mL leukocytes for 30 minutes at room temperature. After incubation, the mixture was layered onto 1 mL of sucrose (20%) and centrifuged at 2,800 *g* for 5 minutes. The leukocyte pellet was then mixed with 200 μL of enhancement solution, and the amount of europium label released into the solution was measured in a time-resolved fluorometer (Delfia; Pharmacia Wallac, Turku, Finland). Nonspecific binding of the label was controlled by preincubation of isolated leukocytes with excess unlabeled monoclonal antibodies against CR3. The final results were expressed as counts per second/10^3 cells.

COMPLEMENT C3a. Concentrations of C3a in plasma were determined by radioimmunoassay according to the manufacturer's instructions (The Upjohn Company, Kalamazoo, MI).

LEUKOTRIENE B_4. To measure leukotriene B_4 (LTB_4), plasma was first acidified with acetic acid to pH 3 to 4. The LTB_4 was then extracted by ethyl acetate and the concentration determined by enzyme immunoassay (Cayman, Ann Arbor, MI).

LEUKOCYTE ELASTASE. Plasma elastase concentrations were quantitated in complex with α_1-proteinase inhibitor by enzyme-linked immunosorbent assay (Merck, Darmstadt, Germany).

In Vitro Study

Whole blood (9 mL) drawn from healthy donors (n = 5) was mixed immediately with 1 mL of 3.8% sodium citrate for anticoagulation. Leukocytes were isolated by combined sedimentation and hypotonic lysis according to the technique previously presented [10]. Zymosan-activated plasma was prepared by incubation of autologous plasma with 1 mg/mL of zymosan (Sigma Chemical Co, St. Louis, MO) for 30 minutes at 37°C. After zymosan particles were separated from plasma by centrifugation at 1,000 *g* for 10 minutes, serial log dilutions of zymosan-activated plasma were made with phosphate-buffered saline solution. Each of the 100-μL phosphate-buffered saline solutions containing different concentrations of zymosan-activated plasma was then incubated with 100 μL of isolated leukocyte suspension for 60 minutes. Finally, CR3 expression on these cells was determined by time-resolved fluoroimmunoassay.

Statistical Analysis

Values for cell counts obtained and biochemical tests done during CPB were corrected for hemodilution using the hematocrit levels measured before bypass. Statistical analysis was performed using Student's *t* test, and the results were expressed as the mean ± the standard error of the mean.

Results

Leukocyte CR3 Receptors

Expression of CR3 on leukocytes increased significantly 5 minutes after the start of CPB compared with the prebypass values ($p < 0.05$). This early peak of leukocyte CR3 expression gradually returned to the prebypass value until release of the aortic cross-clamp. After release of the clamp, a second peak of leukocyte CR3 expression was induced ($p < 0.05$), and this high CR3 expression was maintained to the end of CPB ($p < 0.05$) (Fig 1).

Leukocyte Count

In association with the increased CR3 expression, there was an initial drop in the number of circulating leukocytes 5 minutes after the start of CPB (from 4,9 ± 0.3 × 10^9/L to 4.4 ± 0.3 × 10^9/L; $p > 0.05$). Leukocytosis to about three times the prebypass count developed late during CPB (Fig 2).

Complement C3a

Plasma C3a concentrations increased significantly after the start of CPB to a peak level of 2,210 ± 440 ng/mL

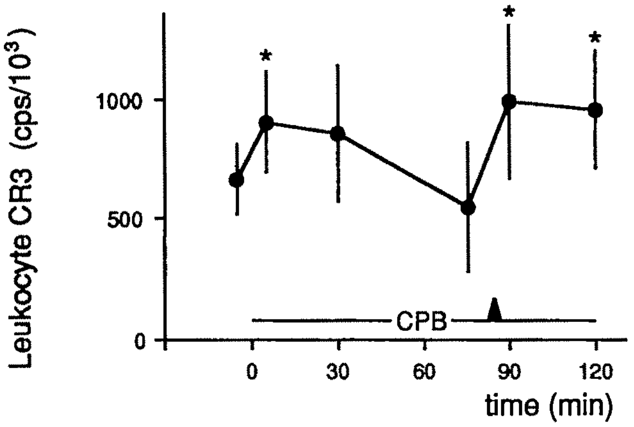

Fig 1. Expression of complement receptors type 3 (CR3) *on leukocytes from patients undergoing cardiopulmonary bypass* (CPB). *The CR3 expression increased immediately after the start of CPB and was followed by a second increase after aortic cross-clamp release* (triangle) *during the late period of CPB.* (* = $p < 0.05$ *versus baseline.)*

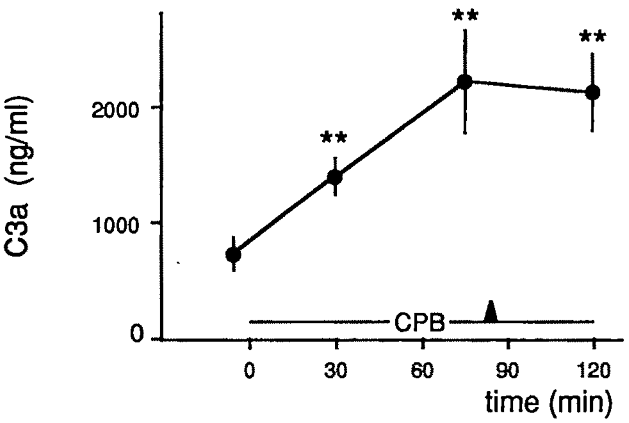

Fig 3. Complement C3a increased significantly after the start of cardiopulmonary bypass (CPB) *and remained high until the end of CPB.* (** = $p < 0.01$ *versus baseline;* triangle = *release of aortic cross-clamp.)*

during CPB ($p < 0.01$). The concentrations remained high until the end of bypass ($p < 0.01$) (Fig 3).

Leukotriene B_4

The level of LTB_4 increased immediately after the start of CPB and remained high thereafter, with an increase 5 minutes after release of the aortic cross-clamp ($p < 0.05$) (Fig 4).

Leukocyte Elastase

There was only a slight increase of elastase in plasma early during CPB. However, the plasma elastase concentration increased significantly 5 minutes after release of the aortic cross-clamp ($p < 0.05$) and remained high until the end of CPB ($p < 0.05$) (Fig 5).

In Vitro Studies

In vitro studies with leukocytes isolated from healthy donors showed that the increased CR3 expression correlated with an increased concentration of zymosan-activated plasma. The CR3 expression on leukocytes increased at a concentration of zymosan-activated plasma as low as 10^{-3} in phosphate-buffered saline solution (vol/vol) with the maximal increase at a 10^{-1} concentration (Fig 6).

Comment

The present study demonstrates that CR3 expression on leukocytes increased immediately after the start of CPB, concomitant with an early sharp increase of C3a. Moreover, a second peak of CR3 expression on leukocytes was induced after release of the aortic cross-clamp and was paralleled by a significant increase of LTB_4 and release of leukocyte elastase.

The rapid leukocyte CR3 expression early during CPB is likely mediated by complement activation, as a dose-dependent increase of CR3 expression was similarly stimulated by zymosan-activated plasma in vitro (see Fig 6).

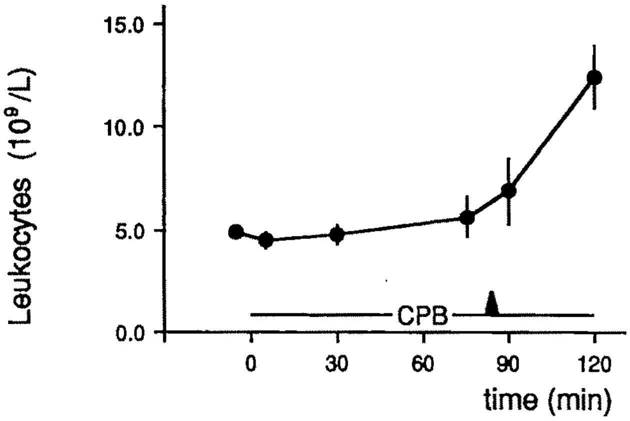

Fig 2. Circulating leukocyte count dropped at the beginning of cardiopulmonary bypass (CPB) *and then had a sharp increase late during CPB.* (triangle = *release of aortic cross-clamp.)*

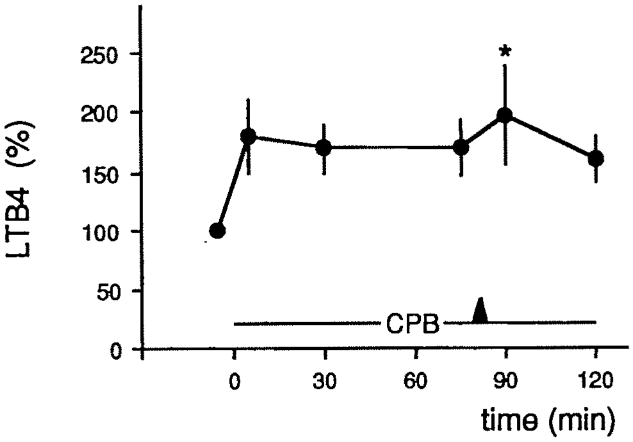

Fig 4. Leukotriene B4 (LTB4), *presented as percentage of baseline value, increased immediately after the start of cardiopulmonary bypass* (CPB) *with the highest level 5 minutes after aortic cross-clamp release* (triangle) *in the late period of CPB.* (* = $p < 0.05$ *versus baseline.)*

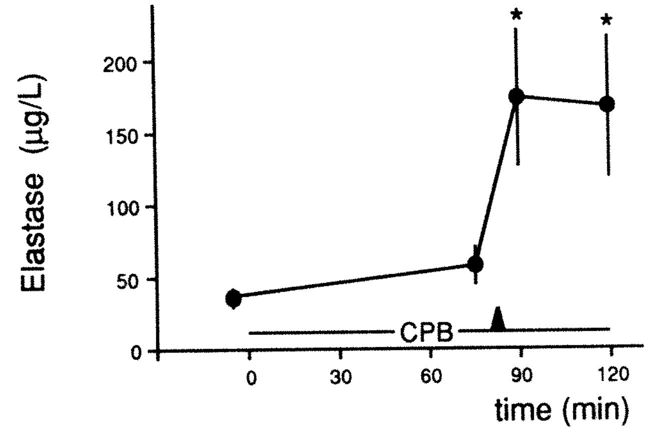

Fig 5. Elastase concentration increased significantly 5 minutes after release of the aortic cross-clamp (triangle) *and remained high until the end of cardiopulmonary bypass* (CPB). *(* = p < 0.05 versus baseline.)*

During CPB, the complement system is indeed activated by blood–material interaction, as reflected by the sharp increase of plasma C3a (see Fig 3). Although leukocyte CR3 expression is known to be induced by C5a, this peptide is difficult to detect because of its very short half-life and rapid binding on PMNs in vivo [5, 7]. In previous studies [7], receptors for C5a have been demonstrated on the surface of PMNs that are involved directly in mediating the chemotactic response of these cells including the changes in intracellular oxygen metabolism and cellular aggregation. Besides these changes, however, the binding of C5a on PMNs also leads to the immediate increase of adhesive receptor expression, such as CR3, and increases leukocyte adhesion [12, 13]. The consequences of the increased leukocyte adherence will be, in the early period of CPB, increased leukocyte adhesion to the surfaces of foreign material. On these surfaces, C3b is chemically bound to the surface hydroxyl groups through ester bonding when the complement system is activated [14, 15]. The expressed CR3 on leukocytes recognizes the inactivated form of C3b (C3bi) on the material surfaces and in turn mediates leukocyte adhesion to the foreign material [16], resulting in a commonly observed pattern of initial leukopenia in patients undergoing both hemodialysis and CPB [4, 5, 17].

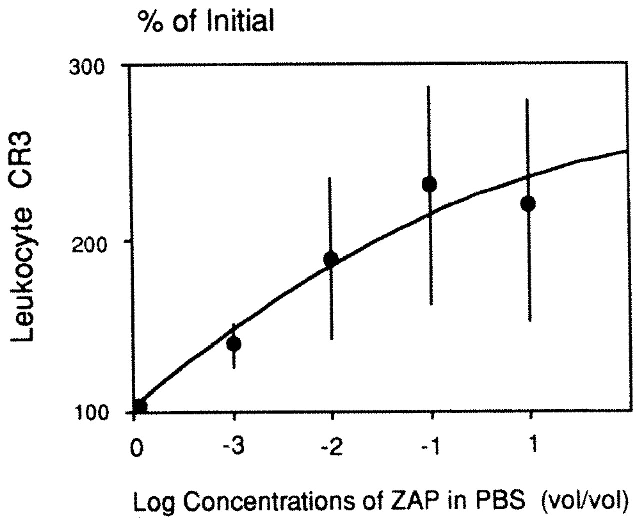

Fig 6. Expression of complement receptors type 3 (CR3) *on leukocytes isolated from donor blood stimulated by zymosan-activated plasma* (ZAP). *The CR3 expression increased with increased concentrations of ZAP.* (PBS = *phosphate-buffered saline solution.)*

The second peak of leukocyte CR3 expression in the later period of CPB is less likely due to the material-dependent complement activation but rather to stimuli that are considered material-independent [18, 19]. After release of the aortic cross-clamp late during CPB, a unique pattern of blood activation is induced presumably by organ reperfusion [19]. The generation of chemotactic mediators such as LTB_4 is enhanced after reperfusion in the late period of CPB, as observed in the present study as well as in others [19, 20]. Actually, LTB_4 is mainly released by the activated leukocytes through the lipooxygenase pathway. However, this lipid peptide is also a strong and fast mediator stimulating leukocyte CR3 expression and mediating leukocyte adhesion to the endothelial cells [21].

On the other hand, release of endogenous endotoxin was found to occur at this specific moment during CPB followed by the generation of tumor necrosis factors [22], both of which are known to be potential stimuli for the expression of adhesive molecules on endothelial cells promoting leukocyte adhesion [23]. As a result, an enhanced interaction between leukocytes and host endothelial cells is induced, leading to intensified leukocyte sequestration and leukocyte-mediated tissue injury [24, 25], the consequence of which tends to be more deleterious than leukocyte adhesion to the material surfaces. It has already been demonstrated in both animal experiments and clinical reports that leukocyte sequestration together with the release of oxygen free radicals occurs massively in the lungs after pulmonary reperfusion [26–28]. This deleterious effect was also demonstrated in the present study by the release of leukocyte elastase, a specific protease mediating endothelial cell injury [29], which increased dramatically after cross-clamp release in the late period of CPB.

In conclusion, the CR3 expression on leukocytes increased immediately after blood contacted the extracorporeal circuit in the early period of CPB. This was followed by a second peak of expression that occurred after reperfusion and was associated with a strong release of elastase known to cause tissue injury. It can therefore be anticipated that if these adhesive receptors on leukocytes could be transiently blocked by monoclonal antibodies or pharmacologically suppressed by other substances [30, 31], the sequential damaging effects of leukocyte-mediated endothelial injury induced by CPB could possibly be diminished or even eliminated.

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Hemostatic Abnormalities in Total Artificial Heart Patients as Detected by Specific Blood Markers

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We retrospectively evaluated the hemostatic system of 13 patients during implantation (2 to 35 days) of the Jarvik 7-70 total artificial heart (TAH). Although all patients were clinically manageable while on the TAH, 5 had excessive generalized bleeding. After the heart transplant procedure, 2 patients had neurological events and 1 patient, thrombosis of the leg. While the patients were supported by the TAH, the routine coagulation assays (prothrombin time, activated partial thromboplastin time, fibrinogen, factor assays, and platelet count) showed slight abnormalities but no correlation to hemorrhagic or thrombotic events. In contrast, plasma and cellular activation markers, which are highly sensitive and specific for hypercoagulability, fibrinolysis, or platelet activation, revealed activation in all patients. Most striking was the marked activation of the fibrinolytic system ($p < 0.05$ to 0.001). Correlations of individual patient data compared with the average TAH group response could be made between excessive enhancement of fibrinolysis (increased D-dimer and tissue plasminogen activator and decreased plasminogen activator inhibitor) and bleeding. A hypercoagulable state (increased fibrinogen and thrombin-antithrombin complex and decreased antithrombin III and protein C), decreased fibrinolysis (decreased tissue plasminogen activator and D-dimer), activated platelets (increased thromboxane B_2), or combinations of these were associated with thrombosis. The hemostatic activation returned to normal 1 day after removal of the TAH. These data suggest that the patient with a TAH requires more sophisticated laboratory monitoring and individualized treatment for excessive fibrinolysis, hypercoagulable state, or platelet activation to avoid thrombotic and hemorrhagic complications.

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The use of the total artificial heart (TAH) as a bridge to transplantation has made possible the survival of patients with end-stage cardiac disease until a donor heart becomes available. The first human implantation was performed in 1969 by Cooley and colleagues [1], and the first successful bridge to heart transplantation was accomplished by Copeland and associates [2] in 1985.

Beginning in 1988, the Jarvik 7-70 TAH (Symbion, Inc, Salt Lake City, UT) has been used in patients at Loyola University Medical Center with end-stage heart failure as a bridge over time until an appropriate donor human heart becomes available. Although these patients and those at other institutions have experienced varying degrees of hemorrhagic complications and occasional thrombotic episodes, the overall successful outcome has highly warranted continued use of the TAH. However, as stated by Joyce and co-workers [3], "although the incidence of transient ischemic attacks and cerebrovascular accidents is much less frequent than initially expected with the permanent use of the TAH, it does continue to be a potential threat during the time of implant."

To further understand what effect the TAH and its associated surgical intervention have on the hemostatic system of this patient population, we have undertaken a study to investigate the hemostatic profile of TAH recipients. Because only limited hemostatic data on a few TAH patients are available [3–8], we chose this screening approach to evaluate specific plasma and cellular markers of thrombotic, fibrinolytic, platelet, and endothelial function. The results of these assays were compared with the results of the routinely ordered coagulation tests (prothrombin time [PT], activated partial thromboplastin time [APTT], fibrinogen, and platelet count).

Because of their nature (specificity of origin and sensitivity in response to stimuli), alterations in these variables indicate the initial changes that occur at specific biochemical sites associated with activation of the hemostatic system, well before any alteration in the PT, APTT, and fibrinogen assays is observed [9–13]. It is now possible to detect not only a hypocoagulable state (leading to hemorrhage) but also a hypercoagulable state (leading to thrombosis). In addition, the cause of the disorder can be identified through these plasma markers. For example, a severe hemorrhage can be caused not only by a lack of coagulation factors or loss of platelet function but also by an excess of fibrinolytic activity. Clearly, the treatment in each case would be different. Furthermore, risk factors and the initial phase of activation can be detected rather than only the major changes to which the PT, APTT, and fibrinogen respond. Through the clinical use of these hemostatic markers, a more defined diagnosis and thus a

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Table 1. Summary of Data on Patients Supported With a Total Artificial Heart

No. Patient	Age (y)	Sex	Days on TAH	Admitting Diagnosis	Status
1	26	M	10	ICM, CAD, MVI, LVD	Died 14 mo after Tx (chronic rejection)
2	52	M	17	Failed Tx	Alive
3	42	M	33	ICM, CAD, postcardiotomy CS	Died 14 d after Tx (multiple CVAs)
4	64	M	14	DCM, CHF, arrhythmias, ventricular tachycardia	Alive
5	62	M	23	ICM	Alive
6	25	M	2	DCM	Alive
7	59	M	2	ICM, acute MI	Alive
8	25	F	2	Postpartum ICM, cardiac arrest	Alive
9	55	M	35	ICM, acute MI, CS	Died 4 mo after Tx (CMV, *Pneumocystis* pneumonia)
10	18	M	6	Giant cell myocarditis	Alive
11	60	F	5	ICM, CAD, CS	Died 8.5 mo after Tx (bronchopneumonia with multiple-organ failure)
12	16	M	2	DCM, MVI	Alive
13	19	M	2	ICM	Alive

CAD = coronary artery disease; CHF = congestive heart failure; CMV = cytomegalovirus; CS = cardiogenic shock; CVA = cerebrovascular accident; DCM = dilated cardiomyopathy; ICM = ischemic cardiomyopathy; LVD = left ventricular dysfunction; MI = myocardial infarction; MVI = mitral valve insufficiency; TAH = total artificial heart; Tx = transplantation.

more targeted treatment of thrombotic and hemorrhagic disorders of TAH recipients should be possible.

Material and Methods

A total of 13 patients (11 male and 2 female) were entered in this study (Table 1) [14]. Patients received the Jarvik 7-70 TAH as a bridge over time until a donor heart became available and was transplanted (range, 2 to 35 days of support; 7 patients $\leq$ 6 days and 6 patients $\geq$ 10 days). The patients ranged in age from 16 to 64 years (mean age, 40 ± 18 years; 6 patients $<$ 30 years old and 5 patients $\geq$ 55 years old). The clinical diagnoses included cardiomyopathy (11 patients: 8 ischemic and 3 dilated), giant cell myocarditis (1 patient), and failed heart transplant (1 patient). Additional associated complications included cardiogenic shock (3 patients), coronary artery disease (3 patients), acute myocardial infarction (2 patients), mitral valve insufficiency (2 patients), ventricular dysfunction (2 patients), and terminal congestive heart failure (1 patient).

While supported by the TAH, all patients were given intravenous heparin sodium to maintain the activated clotting time at 170 to 200 seconds (normal, 70 to 100 seconds) and dipyridamole (100 mg four times a day).

Blood samples were collected in citrate or EDTA (ethylenediaminetetraacetic acid)/indomethacin once daily (early morning draw) from patients while on the TAH. Blood was collected through an indwelling Swan-Ganz catheter. The initial 10 mL of blood was discarded so as not to contaminate the specimen with flush heparin. Blood collection tubes were placed on ice and immediately centrifuged at 2,000 *g* for 20 minutes at 4°C to obtain cell-free plasma. Aliquots of plasma were immediately frozen (−70°C) for analysis within 3 weeks.

The clinical orders for laboratory evaluation included PT, APTT, fibrinogen, fibrin/fibrinogen split products, platelet count, complete blood count, and plasma free hemoglobin. Other tests ordered as needed were thrombin time, antithrombin III (AT III), factors VII, IX, and X, and bleeding time.

For this study, several blood variables specific for coagulation and fibrinolytic, platelet, or endothelial activation were measured:

- Coagulation System Variables
  - PT*
  - APTT*
  - Fibrinogen*
  - Fibrin/fibrinogen split products*
  - Factor assays*
  - Thrombin time*
  - Bleeding time*
  - AT III
  - Protein C
  - Protein S
  - Thrombin-antithrombin (TAT) complex
- Fibrinolytic System Variables
  - D-dimer
  - Fibrinogen degradation products
  - Fibrin degradation products
  - Total degradation products
  - Tissue plasminogen activator (tPA)
  - Plasminogen activator inhibitor (PAI)
  - Plasminogen
  - α_2-Antiplasmin

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* This is a routine clinical order.

Platelet Variables
  Platelet count*
  Platelet factor 4
  Thromboxane B_2 (TxB_2)
  6-Keto prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$)
Endothelium Variables
  tPA
  PAI
  $PGF_{1\alpha}$
Other
  Complete blood count*
  Plasma free hemoglobin*

These variables include activators, inhibitors, and byproducts of biochemical reactions.

The TAH patient group was compared as a whole with a normal population (apparently healthy, nonsmoking, nonobese, and nonmedicated). Further comparisons were made between the TAH–supported patients with complications (hemorrhagic or thrombotic) and the average TAH group response. Statistical analysis was performed by analysis of variance with significance determined at a p value of less than 0.05. These studies were approved by the Internal Review Board of Loyola University Chicago before their undertaking.

Results

While on the TAH, 8 patients (62%) showed no major hemostatic abnormalities, whereas 5 patients (38%) experienced hemorrhagic complications and required an exploratory operation. Because no definite bleeding site was identified at reoperation, the bleeding in these 5 patients was recorded as a generalized coagulation disorder, not a technical problem associated with implantation of the device. These patients received fresh frozen plasma, platelets, cryoprecipitate, or a combination of these.

All patients underwent heart transplantation. After transplantation, 1 patient sustained a massive stroke within 48 hours, 1 patient experienced a transient ischemic attack, and 1 patient had development of venous thrombosis of the leg. The overall long-term survival rate (>1 year after transplantation) of these patients is currently 69% (9/13).

Coagulation System Evaluation

For global screening of coagulation function, the PT and APTT assays were performed in patients supported by the TAH. The values for both assays were slightly prolonged above normal. However, there were no changes throughout the TAH period in patients with or without bleeding complications. The PT values ranged from 13.1 to 14.8 seconds (normal, 10 to 12 seconds) and the APTT values, from 34.3 to 50.3 seconds (normal, 32 to 34 seconds).

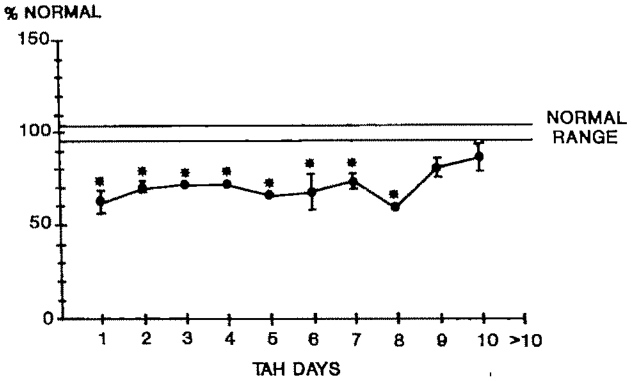

*Fig 1. Daily morning blood plasma samples, collected during the course of total artificial heart (TAH) support, were analyzed for antithrombin III, a plasma inhibitor of coagulation. Results represent a mean ± one standard error of the mean. (*p < 0.05 by t test.)*

Assays for factors VII, IX, and X showed little variation during TAH support. Levels were typically 80% to 100%, except in 1 patient with 45% to 65% levels. The level of factor VIII, a reactive protein, on the other hand, was typically elevated (100% to 200%) in all patients with the TAH. Similarly, fibrinogen values were somewhat elevated compared with normal and actually rose during the days of TAH support from an average of 3.5 g/L (350 mg/dL) to 4.5 g/L (450 mg/dL) ($p < 0.004$ versus normal).

Antithrombin III is an important inhibitor of activated coagulation factor X and thrombin. Levels of AT III were significantly lower than normal, averaging approximately 60% ($p < 0.001$) on the first day (Fig 1). A slight increase of 5% to 10% was noted after the first day on the TAH. Protein C, an inhibitor of factors Va and VIIIa, was also significantly lower than normal, ranging from approximately 28% to 40% ($p < 0.001$) during the first 2 days on the TAH and remaining low in most patients over the first 10 days (Fig 2). Protein S, the cofactor for protein C activation, was low (33% to 42%; $p < 0.001$) during the first 2 days of TAH support but increased to nearly normal levels afterward (see Fig 2).

The TAT complex is formed when coagulation is acti-

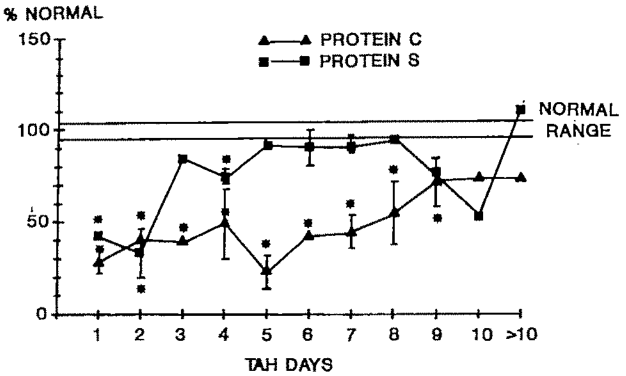

*Fig 2. Daily morning blood plasma samples, collected during the course of total artificial heart (TAH) support, were analyzed for protein C and protein S, two plasma inhibitors of coagulation. Results represent a mean ± one standard error of the mean. (*p < 0.05 by t test.)*

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* This is a routine clinical order.

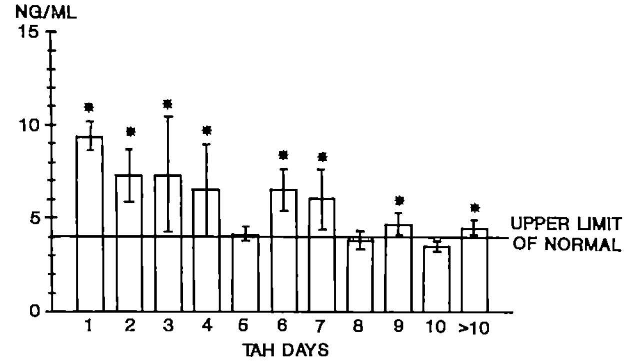

*Fig 3. Daily morning blood plasma samples, collected during the course of total artificial heart (TAH) support, were analyzed for thrombin-antithrombin complex, a marker of coagulation activation. Results represent a mean ± one standard error of the mean. (*p < 0.05 by t test.)*

vated, and the formed thrombin then binds to circulating AT III. The TAT complex is thus a marker of a hypercoagulable state. On days 1 through 3 of TAH support, the TAT complex levels were significantly elevated to 6 to 9 ng/mL (normal, 1 to 4 ng/mL) ($p < 0.001$) (Fig 3). Gradually these levels fell but remained elevated at 4 to 6 ng/mL for up to 10 days on the TAH ($p < 0.001$).

Fibrinolytic System Evaluation

In all TAH patients, levels of fibrin/fibrinogen split products were highly elevated, indicating coagulation or fibrinolytic activation or both. These blood samples were analyzed by newer, more sensitive assays to determine specifically the extent of fibrinolytic activation. Quantitation of the total (fibrin and fibrinogen) degradation products revealed levels of 3 to 7 µg/mL (normal, <0.2 µg/mL) ($p < 0.001$) during the first 10 days of TAH support (Fig 4).

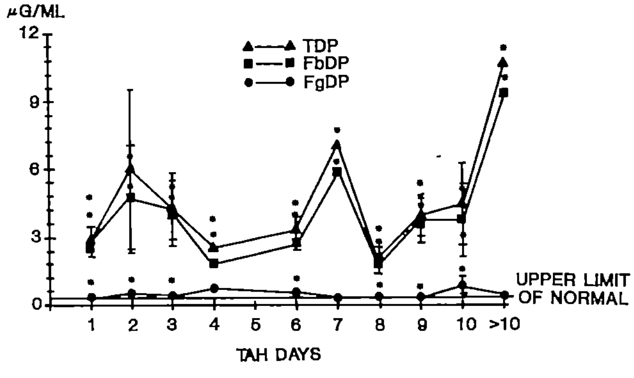

*Fig 4. Daily morning blood plasma samples, collected during the course of total artificial heart (TAH) support, were analyzed for fibrin degradation products (FbDP), fibrinogen degradation products (FgDP), and total degradation products (TDP), the sum of the preceding two variables. These are markers of fibrinolytic system activation. Results represent a mean ± one standard error of the mean. (*p < 0.05 by t test.)*

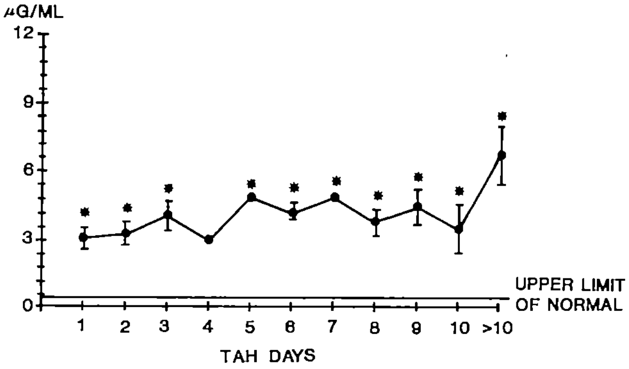

*Fig 5. Daily morning blood plasma samples, collected during the course of total artificial heart (TAH) support, were analyzed for D-dimer, a marker of fibrinolytic system activation. Results represent a mean ± one standard error of the mean. (*p < 0.05 by t test.)*

The levels of fibrinogen degradation products were only slightly elevated with the TAH, 0.3 to 0.5 µg/mL (normal, <0.2 µg/mL) ($p = 0.05$) but remained elevated for 10 TAH support days (see Fig 4). The levels of fibrin degradation products, on the other hand, were highly elevated at 2 to 6 µg/mL (normal, < 0.2 µg/mL) ($p < 0.001$) for all TAH support days (see Fig 4).

D-dimer is currently the most specific blood marker to indicate ongoing fibrinolytic activation. In the TAH patients, markedly elevated levels of D-dimer were measured, 3,000 to more than 5,000 ng/mL (normal, 50 to 300 ng/mL) ($p < 0.001$), throughout the entire 10 days of TAH support examined (Fig 5).

The major components of the fibrinolytic system are plasminogen, the active enzyme that degrades fibrin, and α_2-antiplasmin, an inhibitor of plasminogen. About half of the patients had low levels of plasminogen (40% to 60% of normal; $p = 0.03$) and α_2-antiplasmin (50% to 70% of normal;

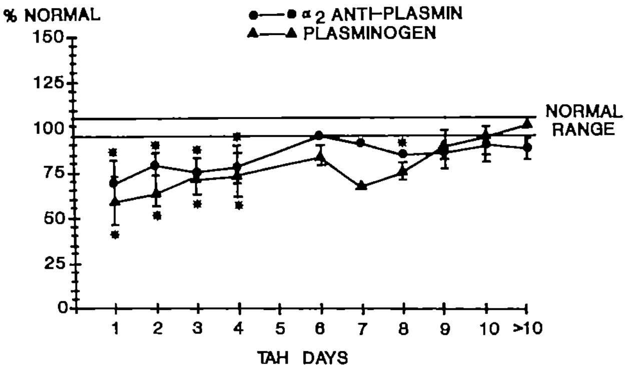

*Fig 6. Daily morning blood plasma samples, collected during the course of total artificial heart (TAH) support, were analyzed for α_2-antiplasmin, an inhibitor of fibrinolysis, and plasminogen, an activator of fibrinolysis. These are markers of fibrinolytic system activation. Results represent a mean ± one standard error of the mean. (*p < 0.05 by t test.)*

p = 0.01). Both variables increased to 90% of normal after 10 days on the TAH (Fig 6).

Levels of tPA, an activator of plasminogen, were significantly elevated in the TAH patients, ranging from 7 to 14 ng/mL (normal, 1.0 to 4.0 ng/mL) ($p < 0.001$) (Fig 7). Three patients showed excessively high levels of tPA (>15 ng/mL). Levels of PAI, the inhibitor of tPA, generally followed a similar pattern as tPA but did not become as elevated. The PAI levels ranged from 3 to 9 ng/mL (normal, 1 to 4 ng/mL) (p = 0.01) (Fig 7). Two patients showed PAI levels higher than 15 ng/mL. There was more variation in the data for PAI than for tPA.

Evaluation of Platelets

The platelet count was normal but showed a slight decrease during the first days on the TAH (90 to 200 × 10^9/L [90 to 200 × $10^3/\mu l$] versus normal, 250 to 350 × 10^9/L [250 to 350 × $10^3/\mu L$]). A trend showing an increase in platelet count after 7 days of TAH support was observed with platelet counts rising to 200 to 300 × 10^9/L (200 to 300 × $10^3/\mu L$). Platelet factor 4 is a substance released from platelets when they are activated. The platelet factor 4 levels were elevated more than tenfold (>100 ng/mL) over normal levels (4 to 8 ng/mL). No differences were observed between patients. These levels remained elevated over the first 10 days of TAH support.

Thromboxane B_2 is a prostaglandin synthesized in the platelet. It is a potent platelet-aggregating agent that is released on platelet activation. The TxB_2 levels were significantly elevated during the first TAH days, ranging from 400 to 500 pg/mL (normal, 90 to 110 pg/mL) ($p <$ 0.001). These levels fell after 4 days of TAH support to about 300 pg/mL but remained higher than normal ($p <$ 0.001) (Fig 8).

6-Keto prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$) is a prostaglandin synthesized in the vascular endothelium. It is a potent anti-platelet aggregating agent. The levels of $PGF_{1\alpha}$ were markedly elevated in TAH patients immediately postoperatively but then fell to 150 to 250 pg/mL (normal, 90 to 110 pg/mL) ($p < 0.001$). This elevated level was not as significant as the elevation of TxB_2, but it remained elevated for 10 TAH support days (see Fig 8).

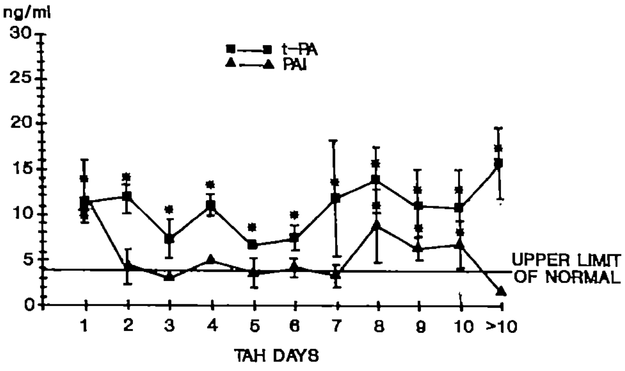

Fig 7. Daily morning blood plasma samples, collected during the course of total artificial heart (TAH) *support, were analyzed for tissue plasminogen activator* (t-PA), *an activator of fibrinolysis, and plasminogen activator inhibitor* (PAI), *an inhibitor of fibrinolysis. These are markers of fibrinolytic system activation. Results represent a mean ± one standard error of the mean.* (*p < 0.05 *by* t *test.*)

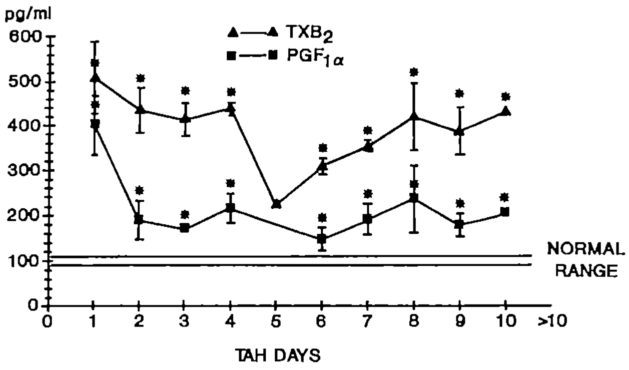

Fig 8. Daily morning blood plasma samples, collected during the course of total artificial heart (TAH) *support, were analyzed for thromboxane* B_2 (TXB_2) *and 6-keto prostaglandin* $F_{1\alpha}$ ($PGF_{1\alpha}$), *markers of platelet activation and inhibition, respectively. Results represent a mean ± one standard error of the mean.* (*p < 0.05 *by* t *test.*)

Comment

In this study of the TAH patient, the possible abnormalities that can occur in the components of the hemostatic system were investigated: the platelets, the fibrinolytic system, the coagulation system, and to some extent the endothelium. The TAH patients were compared as a group during time of support with a normal control group (plasma pool from 5 male and 5 female apparently healthy 25- to 35-year-olds). A surgery control group (ie, patients having completed cardiopulmonary bypass for an elective operation) was not selected for the following reasons: The hemostatic values in the normal population are well established. The typical postoperative response, although investigated in pilot studies, has not been established for all hemostatic variables in all surgical procedures. It is known that changes in some of the hemostatic markers occur with operation [15, 16]; however, whether a relationship to a clinical abnormality in the postoperative phase exists has not yet been defined. This study provides information as to the hemostatic changes that occur as part of the TAH experience, ie, the combination of the patient's disease, operation, use of extracorporeal circulation, catheterization, artificial surface and rheological effects of the TAH, and other medical manipulations (eg, intraaortic balloon pump).

Alterations in hemostatic variables resulting from general surgical manipulation are known to recover to normal levels within 2 days after operation [16]. This pattern was observed for plasminogen and α_2-antiplasmin and even more evidently for PAI and $PGF_{1\alpha}$ in our TAH study. However, the level of the other markers remained consistently elevated with the TAH (up to 35 days postoperatively) and returned to normal the first day after its removal. This pattern suggests that these hemostatic changes were, in fact, due to the TAH. In general, a hypercoagulable state, platelet activation, and, most critical, excessive fibrinolytic activation were present in these patients. Perhaps more importantly, however, a change from the average TAH patient response (group mean) could often be associated with excessive bleeding or clotting disorders.

A hypercoagulable state was determined by the increased level of the TAT complex in most patients. The TAT complex forms when thrombin is generated by coagulation activation. With heparin treatment, however, this interaction is modified. Heparin will enhance the binding between thrombin and AT III but also attenuate the amount of thrombin generated. Overall, in a well-managed surgical patient there will be a moderate increase in the TAT complex level [17]. On the other hand, lower than expected TAT complex levels could be indicative of thrombin or AT III consumption.

In 2 patients, a lower than average TAT complex level was observed for several consecutive days. One patient sustained a stroke and the other, a transient ischemic attack after heart transplantation. In 3 other patients, the TAT levels fluctuated between less than the TAH group mean and the TAH group mean levels. Several days after these fluctuations began, the patients experienced episodes of excessive bleeding from the mediastinum, which responded to treatment with fresh frozen plasma and cryoprecipitate. Patients with no hemorrhagic or thrombotic complications had higher than normal, but steady, TAT levels.

Evaluation of the important inhibitors of the coagulation cascade revealed low levels of protein C, low levels of AT III, and normal levels of protein S in the TAH-supported patients. The low protein C and AT III levels would contribute to the development of a hypercoagulable state. In 1 patient who had a very unstable postoperative course, consistently low protein C levels (30% to 40%) were observed. In addition, 2 patients with consistently higher fibrinogen levels than the TAH group average experienced a thrombotic episode after heart transplantation.

Analysis of the fibrinolytic system with the routine fibrin/fibrinogen split products assay indicated activation of fibrinolysis in all patients at all times. The total degradation products assay, like the fibrin/fibrinogen split products assay, measures the breakdown products of fibrin and fibrinogen. Unlike the fibrin/fibrinogen split products assay, however, the total degradation products assay is quantitative and uses an antibody that recognizes epitopes of earlier generated, smaller particles. D-dimer specifically identifies a breakdown product of cross-linked (polymerized) fibrin. Thus, elevated levels of D-dimer are a clear indication that an organized thrombus had formed, which then underwent lysis (thrombolysis).

Both the D-dimer and total degradation products assays revealed significantly elevated clotting/fibrinolytic activity. Further testing showed that approximately 85% of the total degradation products were derived from the degradation of fibrin, and only 15% were derived from the degradation of fibrinogen. This indicates largely a secondary, not a primary, fibrinolytic state.

To understand what caused this excessive activation, several components of the fibrinolytic system were quantitated. Levels of plasminogen and α_2-antiplasmin, the central enzyme and the inhibitor, respectively, of the system, were only decreased during the early days on the TAH but were normal thereafter. On the other hand, the tPA levels were significantly increased throughout all days on the TAH, and PAI levels were slightly elevated.

Tissue plasminogen activator is the major activator of plasminogen. whereas PAI is the important inhibitor of tPA. The ratio of tPA to PAI in the TAH patients was 2.0 or greater for the group mean. Normally the ratio is 1.0 such that a balance is maintained between the two enzymatic activities. The enhanced level observed in the TAH patient could have been a physiological compensation for the contact (coagulation) and platelet activation stimulated by the artificial surface and rheological effects of the TAH.

In several patients, the enhanced fibrinolysis was associated with bleeding from the mediastinum that was treatable with fresh frozen plasma and cryoprecipitate. Before treatment, these patients had a very elevated tPA level or a lower than TAH group average PAI level. The effect of this was manifested in D-dimer levels higher than the TAH group average.

Conversely, in general, in the patients who experienced clinical thrombosis, the tPA levels were lower than the TAH group mean, the PAI levels were higher than the TAH group mean, and the D-dimer levels were lower than the TAH group mean. In addition, the tPA to PAI ratio was less than 2.0, indicating a lower level of fibrinolytic activity than what was generally observed in the TAH patients. These changes usually preceded the clinical event by several days. One patient had an elevation of fibrinogen degradation products, a finding indicating a primary fibrinolytic state.

To assess platelet activation, TxB_2 and platelet factor 4, both release products from the platelet, were quantitated. In general, all patients had levels elevated above normal during the entire period of TAH support. However, the patient who experienced a transient ischemic attack had a higher level of TxB_2, a very potent platelet-aggregating substance, than the group average. This enhanced activity lasted at least 4 days before the clinical event occurred. Levels of platelet factor 4 were so elevated in all patients that it could not be used as a diagnostic aid. However, its antiheparin activity may have had some clinical significance.

Levels of $PGF_{1\alpha}$, a natural antagonist of TxB_2 because it is a potent anti-platelet aggregating substance, rose slightly with the TAH but returned to normal after its removal. This indicates that there was less than normal protection against the high TxB_2 levels. Although not done in this study, assays for platelet function would have been very interesting to measure.

In hemostasis, the platelet–vascular endothelium interaction is integral to normal function. The endothelium of the TAH patients was greatly stimulated, as suggested by the higher than normal levels of $PGF_{1\alpha}$, tPA, and PAI, all of which are derived from the vascular endothelium. Thus it appears that all aspects of the hemostatic system were greatly activated in the TAH–supported patient, but that the natural balance between the components was still maintained, albeit at a higher level. However, in those patients not responding like the average TAH patient, excessive bleeding was observed. In those patients in whom thrombotic complications developed after transplantation, it is likely that the added stress of the second operation [14], coupled with the risk factors described here, set the stage for the development of these complications.

In the TAH patient, the alterations in the PT, APTT, activated clotting time, and thrombin time assays were useful to monitor heparin therapy. The factor assays and platelet count were useful to evaluate the patients for severe deficiencies that could be treated with blood component therapy. However, these routine assays did not reflect the physiological state of the patient or the efficacy of drug treatment, nor were they able to predict thrombotic or hemorrhagic complications.

The data from this study indicate that patients with a TAH should be evaluated not only by the routine coagulation assays but also by more sensitive plasma markers specific for coagulation (hypercoagulable), fibrinolytic, and platelet activation. In particular, the fibrinogen, protein C, TAT, tPA, PAI, D-dimer, and TxB_2 assays revealed diagnostically useful information.

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Infundibular Septal Defect With Severe Aortic Regurgitation: A New Surgical Approach

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Aortic regurgitation associated with prolapse of an aortic cusp and an infundibular septal defect is caused by the lack of anatomical support for the aortic annulus by the conal septum. This fact is taken into consideration in the new surgical approach that we performed in 5 children 3 to 16 years of age with infundibular ventricular septal defect and severe aortic regurgitation. The ventricular septal defect is closed by a patch anchored to another patch through the prolapsed cusp. This second patch is pulled up with the prolapsed cusp and is then fixed in the aortic wall. In all 5 patients, all clinical signs of aortic insufficiency disappeared, and only minimal aortic regurgitation could be demonstrated by color Doppler mapping.

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Infundibular ventricular septal defect (VSD) complicated by aortic insufficiency was first described by Laubry and Pezzi [1] in 1921. Since then, many different surgical approaches have been developed to treat this malformation [2–7]. The various methods used to assess the grade of aortic regurgitation and the differences in the patient population render it difficult to reliably assess the surgical outcome and follow-up of the various techniques in the literature [5, 6, 8–10]. None of these techniques has proved to be consistently successful in the presence of severe regurgitation. In fact, our previous experience in the management of this lesion was disappointing. Here we propose a new surgical technique for the repair of infundibular VSD complicated by important aortic insufficiency. Patients with mild or moderate aortic insufficiency were excluded from this study.

Material and Methods

Technique

In the syndrome of Laubry and Pezzi [1], aortic insufficiency develops because of the lack of support for the aortic annulus and valve by the conal septum. This causes a progressive prolapse of one aortic cusp, usually the right one, into the VSD. Consequently, the two major features of this syndrome are the lack of support for the aortic annulus and the dilatation of the aortic cusp. Our technique eliminates the first problem by creating a new aortic annulus and giving it a support.

A Dacron velour patch with a semilunar shape is attached to the inferior border of the VSD by continuous suture. In the case of an infundibular defect, the inferior rim of the VSD is generally distant from the conduction system. However, an extension of the defect into the perimembranous septum may be encountered. It can be recognized by the existence of a continuity between the inferior border of the VSD and the tricuspid valve, and in this case, the usual precautions to prevent lesions of the conduction system should be applied.

Then U stitches are passed through the upper border of the patch and through the prolapsed cusp (Fig 1, point *B*). Because there is no visible landmark between the aortic wall and the valvular tissue, these stitches are placed at the level that seems appropriate to reshape the prolapsed cusp. The stitches are then attached to a second patch, which also has a semilunar shape and is in a superior position to the first patch, thus creating a sandwich of patch, valvular tissue, patch. The second patch is fixed in the sinus of Valsalva, below the coronary ostium (see Fig 1, point *A*), thereby pulling up the whole structure so as to bring the free border of the cusp to the level of the two other cusps. The enlargement of the free border of the cusp is treated by plication of the valvular tissue next to the commissures (Fig 2).

Patient Population

Between May 1990 and January 1991, 5 patients between 3 and 16 years of age with an infundibular VSD and severe aortic insufficiency underwent surgical repair using the "sandwich" technique. The diagnosis was made in all patients by transthoracic echocardiographic color Doppler examination. Two patients who had associated anomalies (pulmonary stenosis with partial anomalous pulmonary venous drainage into the left superior vena cava in 1 and subaortic stenosis in the other) underwent cardiac catheterization. The degree of aortic insufficiency was clinically assessed by evaluating the diastolic murmur and measuring the differential blood pressure. Because the VSD was

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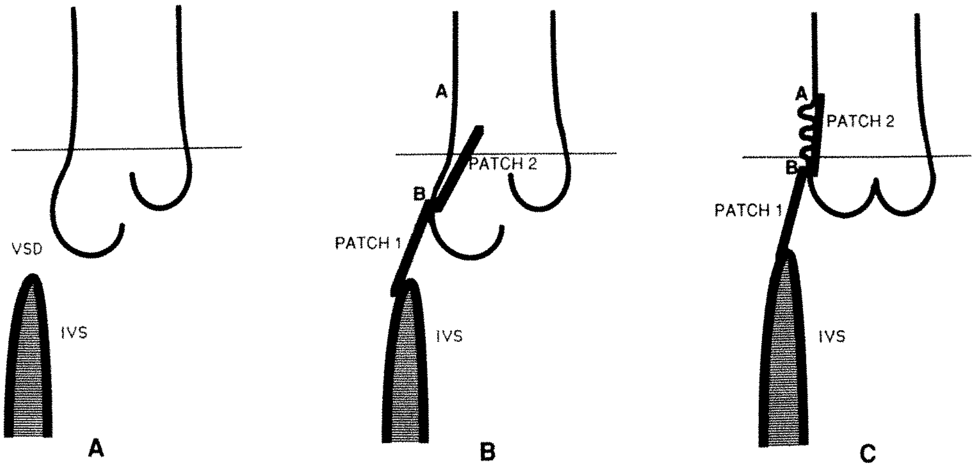

Fig 1. The surgical technique. (A) Anatomy of the syndrome: prolapse of the aortic cusp, which occludes the ventricular septal defect (VSD) almost entirely. The horizontal line shows the level chosen to reconstruct the aortic annulus. (B) The first patch is positioned to close the VSD, and the inferior border of the second patch is anchored. (C) The cusp is lifted up, and the second patch is fixed in the aortic wall. Note the reduction in the distance between points A and B. (IVS = interventricular septum.)

almost entirely occluded by the prolapsed aortic cusp in every patient, the left-to-right shunt probably did not influence the left ventricular size. Therefore, the left ventricular diastolic diameter, measured by echocardiography, was considered to be the most useful variable to evaluate the importance of aortic regurgitation. It was judged severe in all patients (Table 1).

Cardiopulmonary bypass was performed with moderate hypothermia. Myocardial protection was always achieved by infusion of cardioplegia into the coronary ostia.

Results

There were no deaths, and the perioperative course of each patient was uneventful. After operation, the diastolic murmur disappeared, the differential blood pressure returned to normal values, and the left ventricular diameter was markedly reduced in all patients (see Table 1). Only minimal aortic regurgitation was detected by color-Doppler flow mapping in all patients. These variables remained stable over the short follow-up (2 to 11 months).

Comment

Infundibular septal defect associated with severe aortic incompetence remains a difficult surgical problem. The lack of support of the aortic valve by the conal septum, which is the anatomical and physiological basis of the complex [11-15], is taken into consideration by our approach. Many techniques have been developed over the past 30 years to repair this lesion. The evaluation of their results is very difficult [7] because the variables used in

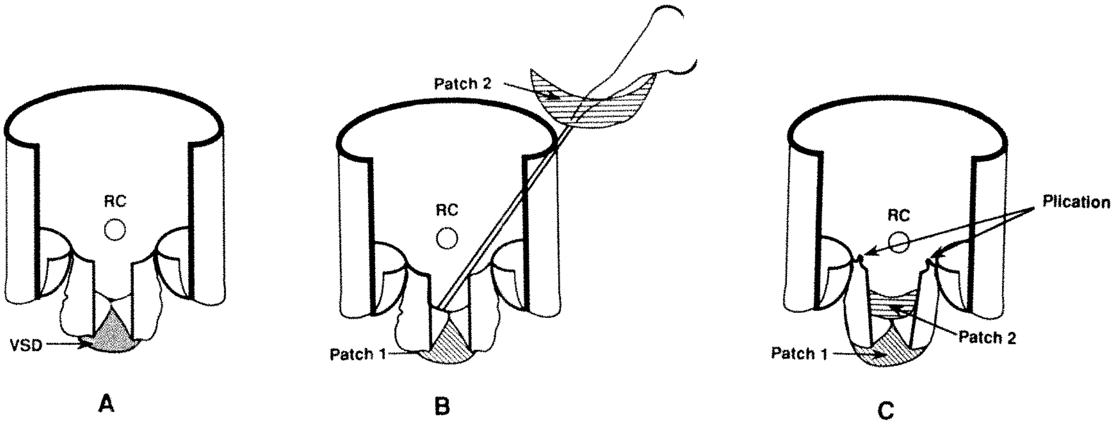

Fig 2. (A) The defect is shown, with the right coronary cusp opened to illustrate the internal part of the cusp. (B) The first patch is fixed to the superior border of the ventricular septal defect (VSD). Then U stitches are passed through the superior border of the patch and through the prolapsed cusp. With these stitches, the inferior border of the second patch is fixed in the internal part of the cusp under the right coronary ostium (RC). (C) After surgical correction, the second patch is fixed in the aortic wall, and the free border of the cusp is reduced by plication of the valve tissue next to the commissures.

Table 1. Clinical and Echocardiographic Data

Patient No.	Age (y)	Blood pressure (mm Hg)		Diastolic Murmur		LV Diastolic Diameter (mm	
		Preop	Postop	Preop	Postop	Preop	Postop
1	3	110/50	120/70	2/6	None	55	41
2	4	120/40	100/70	3/6	None	48	32
3	8	120/60	120/70	2/6	None	51	44
4	9	100/50	110/80	2/6	None	45	41
5	16	120/50	120/80	2/6	None	51	45

LV = left ventricle.

the reports are not comparable. The technique proposed by Trusler and associates [4] was the first to yield convincing surgical results. Recently Chauvaud and coworkers [6] reported good results with a different technique first described by Carpentier [16]. However, the relationship between the severity of preoperative aortic regurgitation and the outcome of valvuloplasty has hardly been considered in the literature.

It is our experience and that of others [5, 7, 14, 15] that simple closure of the VSD in cases of mild aortic regurgitation can be sufficient to reduce or abolish the valvular defect. It should be emphasized that all patients in our series had severe aortic regurgitation. We think the sandwich technique is indicated only when the incompetence is due to prolapse of the aortic valve. In fact, 1 additional child with infundibular VSD and severe aortic regurgitation did not have an important cusp prolapse and underwent operation using the conventional approach with good results.

We do not know whether this technique is applicable to patients with perimembranous defect. In this subset, the prolapse is generally located at the level of the commissure between the noncoronary and the right coronary cusp, and this mechanism does not favor our technique. However, if the pathogenetic mechanism of the valvular insufficiency is the prolapse of a cusp, there is no reason why this technique should not be applied.

All 5 patients operated on with the sandwich technique had very satisfactory results in the immediate postoperative period. Even with massive aortic regurgitation the technique proved useful; in fact, patient 2, who had all the clinical signs of major aortic insufficiency and acute cardiac failure, had a highly satisfactory result. Even with color Doppler mapping it was difficult to identify minimal residual aortic regurgitation.

Our findings are still preliminary, and the long-term results still must be evaluated, with special attention given to the stability of valvular function and the absence of deformation of the annulus with growth. However, in view of the disappointing experience with other techniques, our results appear encouraging.

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Bronchovascular Mucormycosis in the Diabetic: An Urgent Surgical Problem

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This report reviews the successful surgical experience with a diabetic patient with bronchial obstruction due to Mucorales infection. A review of the reported medical and surgical experience is included. The danger of a lethal pulmonary hemorrhage makes early surgical intervention mandatory.

(Ann Thorac Surg 1992;53:854–5)

The combination of mucormycosis and diabetes mellitus causes a well-defined clinical disorder of the bronchus and pulmonary vessels that if unrecognized can result in a fatal hemorrhage. This report contains a review of the experience with the medical and surgical treatment of bronchovascular mucormycosis in the diabetic, illustrated by the successful surgical management of a patient with this rare but potentially lethal disease.

Case Summary

A 50-year-old diabetic man was admitted because of a cough and fever of 5 days' duration. The diabetes mellitus was easy to control with insulin. Five months before he coughed up a small amount of blood.

Physical examination showed his temperature to be 38.9°C. Rales were present posteriorly in the left lower chest. He had hypesthesia in a stockinglike distribution over both legs. Laboratory values revealed a blood sugar level of 6.9 mmol/L (124 mg/dL), but levels up to 22.2 mmol/L (400 mg/dL) were recorded at various times. The blood level of potassium was 4.2 mmol/L (4.2 mEq/mL), the chloride level was 108 mmol/L (108 mEq/mL), and the creatinine level was 79.6 μmol/L (0.9 mg/dL). The urine was negative for ketone bodies and glucose. The chest film showed an area of consolidation in the basilar segments of the left lower lobe.

A bronchoscopic examination revealed the left lower lobe bronchus to be obstructed with a plug of yellowish cheesy material. A portion of the plug was removed. It showed a network of branching pleomorphic nonseptate hyphae typical of Mucorales. After 2 days of treatment with amphotericin, 0.3 mg/kg per day, the patient's left lower lobe was removed without difficulty. After operation, he was given amphotericin daily at the same dosage over the next 14 days. The patient was discharged on the 14th postoperative day.

The left lower lobe bronchus was partially necrotic and contained a 1 × 1-cm cavity with a large pulmonary artery adjacent to it, partially necrotic and occluded by a thrombus. Interspersed within the thrombus, the vessel wall, and bronchus were many organisms similar to those noted in the specimen removed at bronchoscopy. Cultures were negative.

A year later his chest film did not show signs of recurrence.

Comment

When the patient's problem of bronchial obstruction from mucormycosis was recognized, and after only a short 2-day period of amphotericin therapy, the left lower lobe

Table 1. Surgical Treatment by Excision

Reference	Age (y)	Sex	Biopsy	Amphotericin	Acidosis	Bled	Operation	Results
[1]	20	F	Yes	No	Yes	No	Lobe	Alive
[2]	23	F[a]	No	No	No	Yes	Lobe	Alive
[3]	15	F	No	No	Yes	No	Lobe	Alive
[4]	48	F	No	No	No	No	Segment	Alive
[5]	47	M	No	Yes	No	No	Segment	Alive
[6]	52	F	Yes	Yes	Yes	No	Lobe	Alive
[7]	55	M	Yes	No	No	No	Segment	Alive
[8]	13	F	No	No	No	No	Lobe	Alive
Present study	50	M	Yes	Yes	No	Yes	Lobe	Alive

[a] Diabetes developed in this patient 1 year postoperatively.

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Table 2. Medical Treatment

Reference	Age (y)	Sex	Biopsy	Amphotericin	Acidosis	Bled	Results
[10]	29	M[a]	Yes	Yes	Yes	Yes	Died
[11]	59	F	No	No	Yes	Yes	Died
[12]	33	M[b]	Yes	No	No	Yes	Died
[13]	64	M	No	No	Yes	Yes	Died
[14]	38	F[c]	Yes	Yes	Yes	No	Alive
[15]	57	F[d]	Yes	Yes	No	Yes	Died
[16]	12	F	No	NK	NK	NK	Died
[17]	14	M	No	No	No	Yes	Died
[18]	Adult[e]		Yes	NK	NK	Yes	Died
[19]	65	M	No	Yes	No	No	Alive
[20]	14	F[f]	Yes	Yes	Yes	Yes	Died
[21]	20	M	Yes	Yes	No	No	Alive

[a] Died 17 days after biopsy. [b] Died 5 days after biopsy; had cavernostomy. [c] Bronchostenosis—rhinocerebral infection. [d] Died 4 days after biopsy; intrabronchial amphotericin. [e] Age and sex not given. [f] Died 3 days after biopsy.

NK = not known.

was removed because of the fear of an impending serious pulmonary hemorrhage.

The diagnosis of mucormycosis was established in our patient by the nonseptate appearance of the Mucorales on sections obtained from the fungus mass in the bronchus. It is unusual to be able to culture the fungus from either sputum or the surgical specimen.

Table 1 summarizes the experience of several observers with resection in the diabetic for bronchovascular mucormycosis. All patients survived. Three of the patients received amphotericin. Spread or recurrence of the infection after operation has not been reported.

The first diabetic patient cured of mucormycosis was a child with the rhinocerebral form treated by Harris [9] using only careful management of the severe diabetes. With bronchovascular mucormycosis in the diabetic treated medically, control was attempted in 4 of 11 patients with amphotericin (Table 2). Two of the 4 died as did all the other medically treated patients. Five of 8 who bled had a bronchial biopsy a few days before death. In view of this experience, care should be taken to only remove a part of the fungus ball and not include the bronchial wall.

In conclusion, bronchovascular mucormycosis and diabetes makes a potentially lethal combination because of the likelihood of hemorrhage due to the vascular involvement. Although the presenting symptoms may be due to bronchial obstruction, the danger of bleeding precludes the consideration of conservative treatment. Pulmonary resection performed almost as an emergency procedure is the proper treatment.

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Sequential Silastic and Expandable Metal Stenting for Tracheobronchial Strictures

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The risks and limitations of surgical resection and reconstruction for tracheobronchial strictures demand consideration of other therapeutic options that can alleviate the distressing symptoms of tracheobronchial obstruction. One alternative is to stent the obstructive lesion until surgical advances allow primary reconstruction or replacement of the critically diseased airway or until an ideal endoprosthesis is found. The latter requires uniformity in the distribution of expansile force, conformability and stability within the tracheobronchial tree, and ease of placement. Here we report our experience with the placement of expandable metal stents (Wallstent) used in conjunction with our Silastic (Dow Corning) endobronchial stents in 5 patients with recurrent tracheal or bronchial strictures. The major site of obstruction was the trachea in 1 patient and a main bronchus or both bronchi in 4 patients. Three patients had a benign bronchial stricture (anastomotic stricture in 2, idiopathic polychondritis in 1), and 2 patients had an obstructive airway neoplasm. Placement of the stents was performed under rigid bronchoscopic guidance. We had no complications from our technique of stenting. There has been no evidence of restenosis or occlusion within the stented segment of airway. The complementary use of expandable metal and Silastic endobronchial stents provided symptomatic and functional improvement in our patients during follow-up ranging from 5 to 24 months.

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The management of recurrent tracheobronchial obstruction becomes an increasingly important problem if a tracheobronchoplastic operation is not deemed possible. A plethora of therapeutic options are available and include bronchoscopic dilations, endobronchial resection [1], and, more recently, laser therapy [2] and a variety of silicone stents [3–5]. In the case of malignant obstructions, additional palliation can also be achieved with chemotherapy and endobronchial radiotherapy [6]. The relative indications for each of these treatment modalities change with technological advances. Therefore, more effective treatment regimens will either complement or displace some currently used invasive palliative procedures that are usually effective only for the short term.

A self-expanding metal stent (Wallstent) has been used in vascular stenosis [7] and biliary [8] and urethral strictures [9] with encouraging clinical results. The refinement associated with the design of this expandable metal stent has led us to investigate its possible use in improving tracheobronchial patency in patients with benign or neoplastic airway obstruction.

Material and Methods

We have used the sequential stenting technique to be described in 5 patients. Three had a benign bronchial stricture and 2, malignant bronchial strictures (Table 1).

Construction of Silastic Endobronchial Stent

The customized stent is made using an appropriate length of the vertical limb of a 10- to 14-mm Silastic (Dow Corning) Montgomery T tube, and the proximal and distal collars are made from short segments of a slightly larger T tube [4]. The collars were at first glued to the stent, but the curing time delayed the procedure, and they are now sutured to the ends of the stent.

Construction of Wallstent

The Wallstent (Medinvent SA, Lausanne, Switzerland) is made of filaments of a biomedical cobalt-based super alloy braided in the form of a tubular mesh (Fig 1). It is loaded on a delivery catheter 9F in diameter and constrained in its compressed form by invagination in a plastic membrane. The retraction of this membrane with hydraulic assistance permits the gradual release of the endoprosthesis, which expands and shortens to achieve its predetermined form. The expansion will continue if the caliber of the narrowed airway is less than that of the unconstrained stent. The Wallstent is available in a variety of diameters and lengths.

Placement of Silastic Endobronchial Stent and Wallstent

Before placement of a stent, rigid bronchoscopy under general anesthesia provides the final evaluation of the tracheobronchial anatomy. We prefer a rigid bronchoscope for reasons of safety and clear visualization, as it permits instrumental dilation, controlled ventilation in the presence of a suboptimal airway, and aspiration of blood and secretions. Atropine sufate is given as premedication. Anesthesia is induced with propofol and fentanyl and maintained with propofol infusion during the proce-

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Table 1. Summary of Clinical Data for the 5 Patients With Strictures

Patient No.	Age (y)	Sex	Cause of Bronchial Stricture	Site of Stricture	Treatment Before Metal Stenting
Patients With Benign Bronchial Stricture					
1	68	M	Anastomotic stricture after sleeve resection	Right main bronchus	Diathermy resection, dilations, Silastic stenting (15 mo)
2	49	F	Right single-lung transplant for fibrosing alveolitis	Right main bronchus	Dilations, Silastic stenting (18 mo)
3	39	F	Idiopathic chrondritis	Left main bronchus	Dilations, diathermy resection, Silastic stenting (4 mo)
Patients With Malignant Bronchial Stricture					
4	42	M	Inoperable large cell carcinoma	Right and left main bronchi	Radiotherapy, laser resection, Silastic stenting (displaced)
5	41	M	Adenoid cystic carcinoma	Lower trachea and both main bronchi	Tracheal resection, chemotherapy, radiotherapy, dilations, diathermy resection

dure. Muscle relaxation is achieved with atracurium besylate, and ventilation is by the Sanders Venturi system.

The technique of Silastic endobronchial stent placement has been described [4]. Once the stricture has been dilated, the caliber and length of the Silastic stent required can be assessed and a suitable stent fashioned. The stent is forced into position using the rigid bronchoscope to push it over a bougie, and the final position is adjusted with biopsy forceps. The Silastic stent can be easily removed using biopsy forceps if stent replacement or assessment of the stricture site is necessary.

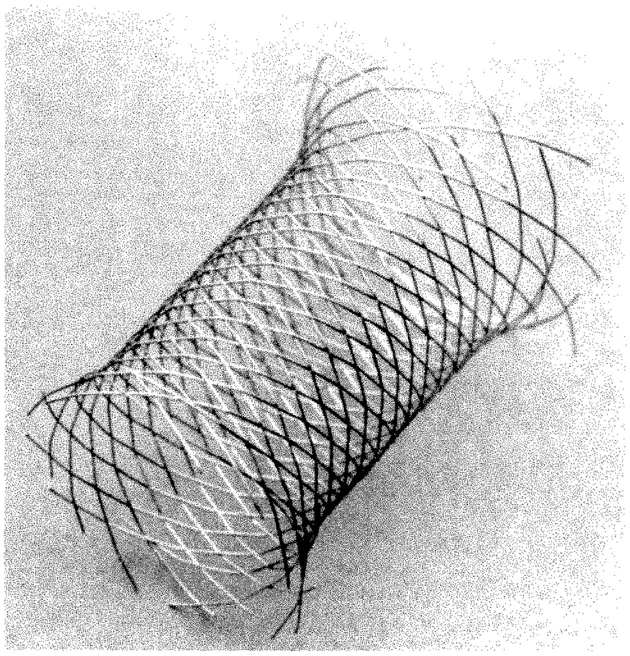

Fig 1. The self-expanding metal stent (Wallstent).

The Wallstent, mounted in its compressed form on the delivery catheter, is passed through the rigid bronchoscope and advanced across the stricture under telescopic control. No fluoroscopic guidance is required. During deployment, the application of hydraulic pressure within the delivery catheter permits gradual retraction of the membrane, allowing release and expansion of the constrained Wallstent. The expansile ends prevent any potential stent migration. However, the metal stent can be removed, with some difficulty, by extracting the metal filaments individually. To date, we have not encountered this problem.

Application of Silastic and Metal Stents

In the 3 patients with severe benign bronchial stricture, an optimal lumen was created with diathermy resection, multiple dilations, or both before the appropriate-sized Silastic stent was inserted. The covered surface of the Silastic stent prevented any airway obstruction from excessive granulation tissue at the stricture site. During follow-up, the Silastic stent was cleaned or replaced when mucous accretions developed within it. Progressively larger Silastic stents were used to maintain the clinical improvement and allowed the inflammatory tissue to mature. This resulted in a smooth, firm stricture more suitable for placement of a metal stent. The ease of removal of the Silastic stent permitted reassessment of the

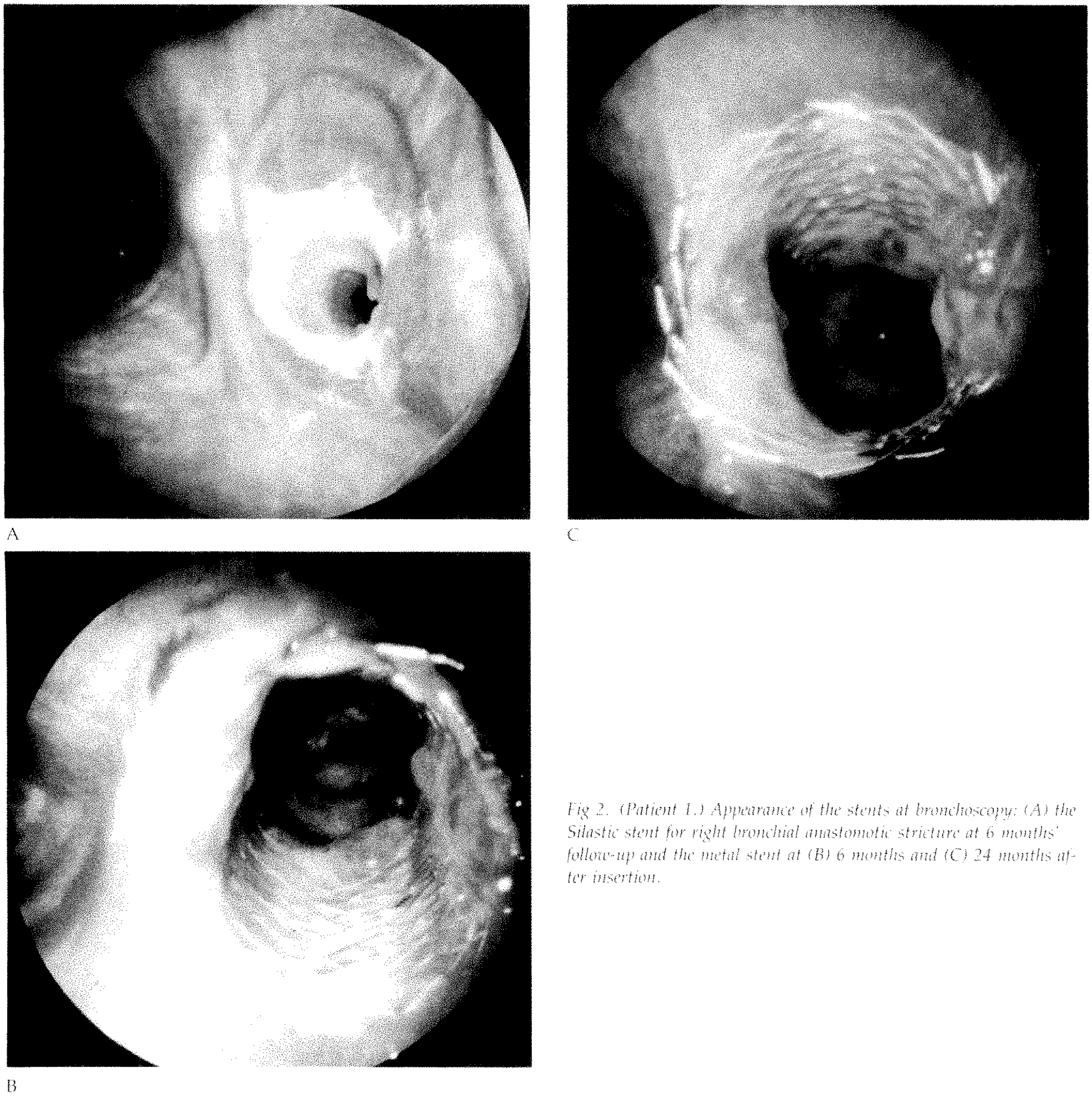

Fig 2. (Patient 1.) Appearance of the stents at bronchoscopy: (A) the Silastic stent for right bronchial anastomotic stricture at 6 months' follow-up and the metal stent at (B) 6 months and (C) 24 months after insertion.

stricture for possible surgical reconstruction. If this was not thought feasible, expandable metal stenting was undertaken as a long-term measure once the mucosal inflammation had subsided on the basis of its endoscopic appearance, (Fig 2).

The application of stents for malignant airway obstruction is different from that for benign stricture. The initial use of a metal stent is more secure for soft tumor tissue, which does not sufficiently grip the Silastic stent. However, the inherent disadvantage of the metal stent is its inability to prevent an intraluminal tumor from growing through the stenting mesh. The covered surface of the Silastic stent reduces the possibility of this happening, and other palliative measures can be used to intervene if necessary. More than one stent can be implanted to cope with long strictures or tracheal bifurcations.

Results

In the 3 patients with severe benign bronchial stricture, insertion of the Silastic stent was associated with marked improvement in symptoms, radiological findings (Fig 3), and breathing capacity (Table 2). The mean forced expiratory volume in 1 second and the mean forced vital capacity before stenting were 1.3 L and 2.1 L, respectively, and after a mean period of 14.3 months of Silastic

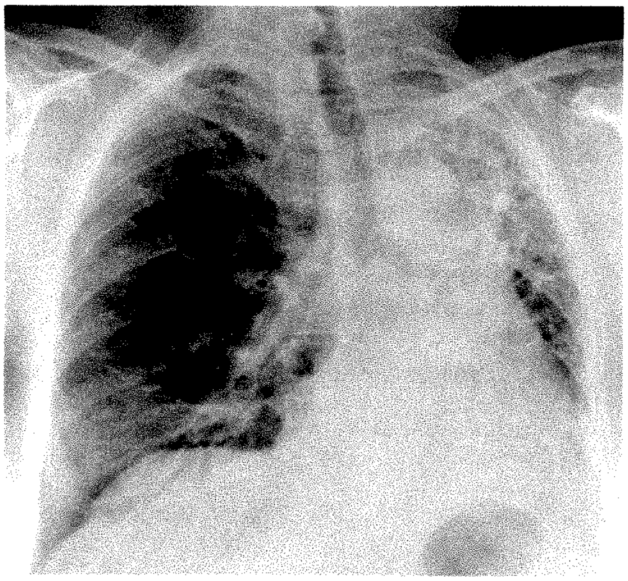

Fig 3. (Patient 2.) Chest radiograph showing the right single-lung transplant after implantation of a metal stent for bronchial anastomotic stricture.

stenting, the mean forced expiratory volume in 1 second had increased to 2.2 L and the mean forced vital capacity, to 3.6 L. Once a metal stent had been placed, the functional improvement was sustained over a mean follow-up of 13 months (see Table 2).

In patient 4, who had carcinomatous infiltration of the right main bronchus and extensive mediastinal involvement, the left main bronchus was also narrowed by extrinsic tumor compression. The distal right bronchial tree appeared to be a tapering, irregular tube of tumor extending down into a large abscess cavity. A Silastic stent was inserted into the right main bronchus but provided only very temporary palliation because of proximal displacement of the stent after bouts of vigorous coughing. It appeared that the soft tumor tissue did not sufficiently grip the Silastic stent. Metal stents were inserted and opened up both main bronchi, providing useful palliation. The patient was discharged home with marked symptomatic improvement. However, his general condition gradually deteriorated over the following 5 months, and he died of carcinomatosis.

Table 2. Changes in Forced Expiratory Volume in 1 Second and Forced Vital Capacity With Sequential Stenting in 3 Patients With Benign Bronchial Stricture[a]

Procedure	Stenting Time (mo)	FEV_1 (L)	FVC (L)
Before stenting	. . .	1.3 (0.5–1.7)	2.1 (1.0–2.8)
Silastic stenting	14.3 (4–24)	2.2 (1.8–2.7)	3.6 (2.4–4.9)
Metal stenting	13 (6–24)	2.4 (1.9–2.7)	3.4 (2.4–4.4)

[a] Data are shown as the mean with the range in parentheses.

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

In patient 5 (forced expiratory volume in 1 second, 1.7 L; forced vital capacity, 3.4 L), an adequate tracheal lumen was created with diathermy resection to allow insertion of individual metal stents into the lower trachea and both left and right main bronchi. However, when seen 2 weeks later, he was breathless on moderate exertion, and at bronchoscopy, tumor was seen growing at the gap between the tracheal and bronchial metal stents. A Silastic endobronchial stent was inserted to bridge the gap between the two metal stents and 6 weeks later, was replaced by another metal stent. This maneuver led to considerable reduction in symptoms, as reflected in the improved forced expiratory volume in 1 second and forced vital capacity (2.1 L and 3.8 L, respectively) at 9 months' follow-up.

There were no complications related to our stenting technique, and both types of stents have been well tolerated. There has been no evidence of restenosis or occlusion within the stented segment of airway.

Comment

Recurrent tracheobronchial strictures have introduced management problems because of the current availability of multiple therapeutic procedures. Technological innovations have provided some attractive options such as laser therapy [2], endobronchial radiotherapy [6], and a variety of silicone [3–5] and expandable metal stents [10–12] suitable for different types of tracheobronchial obstruction. These palliative procedures must be appropriately used, as patency of the tracheobronchial tree is essential for the recovery of previously compromised pulmonary function and elimination of sepsis.

The use of endobronchial stenting represents an important advance in the management of inoperable tracheobronchial strictures [5]. Our early experience [4] with Silastic endobronchial stents for anastomotic stricture has been successful over the short term, as the patients showed improvement in respiratory symptoms and function. These stents are not suitable for neoplastic airway obstruction, as soft tumor tissue does not grip the Silastic stent and it can be displaced. However, this stent can prevent the protrusion of tumor seen with the metal stents.

There are a number of other disadvantages making Silastic stents unsatisfactory for long-term use. The relatively thick silicone wall of the material results in a low internal to external diameter ratio. The stents tend to occlude as mucous accretions form lamellae within them. Therefore, regular bronchoscopic checks are necessary to see whether the stent needs cleaning, or replacement. Theoretically, expandable metal stents offer a better solution for long-term use. Nevertheless, we continue to find Silastic stents valuable, particularly as part of our sequential stenting approach.

The self-expanding metal stent has been used with good results in cases of vascular stenosis [7], biliary stricture [8], and urethral [9] stricture. The expandability, flexibility, and epithelialization within the wire mesh of the metal stent make it appealing for extended use in airway obstruction. The metal stent has a wider lumen than the Silastic stent of the same external diameter, and the spring action of the metal stent increases the size of the stented intraluminal diameter with no substantial inflammatory reaction. Unlike the Gianturco stent [10], the expansile ends of the Wallstent do not require hooks to prevent stent migration. In addition, the Wallstent is made of multiple metal filaments, which, in theory, may provide a larger surface area for stronger radial expandability. The technique of stent insertion is straightforward, and the stent position can be assessed by routine chest radiography and check bronchoscopy if clinically indicated.

Caution should be exercised in recommending use of the metal stent for "inflammatory" strictures, as the protrusion of granulation tissue through the wire mesh of the stent may occlude the lumen. Our sequential stenting approach—using a Silastic stent as the first stage to allow the inflamed area to heal and then replacing it with a self-expanding metal stent—is therefore valid.

In patients with critical airway obstruction, the caliber of the stent needed can be assessed only after other endoscopic steps, such as diathermy resection and bougienage, have created an optimal lumen. The Silastic stents can be made to fit quickly using materials readily available in the operating theater, whereas the correct size of metal stent may not be instantly available. The natural history of some benign stenoses is not known and can be assessed only over time. The Silastic stents can be removed if they are no longer needed or if it is necessary to check whether permanent stenting is required. A removable silicone stent can be inserted as a therapeutic trial if airway stenosis is multifactorial or if several stenoses coexist and it cannot be ascertained which, if any, is important in the patient's dyspnea. A tight stricture may be dilated a number of times before the largest stent possible is inserted. Progressively larger stents can be used to maintain this stepwise improvement between bronchoscopies.

An inflammatory stricture, particularly one resulting from anastomotic dehiscence, will initially be soft and surrounded by granulation tissue. This tissue does not hold a stent well, and the inflammatory tissue can grow through the interstices of metal stents. A Silastic stent provides a barrier to tissue ingrowth while the inflammatory tissue matures. The resultant fibrous stricture is then suitable for metal stenting once the need for long-term stenting has been demonstrated and when the definitive dimensions of the stricture are apparent. Our 3 patients with benign "inflammatory" bronchial stricture have benefited from our sequential stenting approach.

With inoperable malignant tracheal tumor (patient 4), the metal stent has proved to be valuable for prolonged relief of distressing respiratory symptoms. In the patient (patient 5) with inoperable large cell carcinoma of the right lung and obstructive pneumonia, the metal stent allowed drainage of purulent secretions distal to the airway obstruction, reducing sepsis and improving the overall well-being even if there was no major improvement in lung function. The metal stent is uncovered and theoretically cannot prevent recurrent obstruction caused by the ingrowth of intraluminal tumor protruding through the wire mesh. However, we had no stent occlusion in our 2 patients with malignant airway obstruction. There has been a report [12] of the use of a nylon and polyvinyl chloride–covered metal stent as a protective measure against tumor protrusion.

The growing problems of neoplastic and benign airway obstruction provide an opportunity for the judicious application of tracheobronchial stenting. The availability of self-expanding metal stents ensures another therapeutic option for thoracic surgeons facing difficult tracheobronchial strictures. However, the long-term results remain to be defined. We recommend the sequential use of Silastic and expandable metal stents to optimize the management of benign "inflammatory" tracheobronchial obstruction.

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A Model of Left Ventricular Dysfunction Caused by Intracoronary Adriamycin

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Experimental evaluation of new therapy for congestive heart failure has been hampered by the lack of a simple and reliable animal model of heart failure. This study was undertaken to develop a canine model of chronic left ventricular dysfunction. A left thoracotomy was performed in 9 adult mongrel dogs. A 1.5-mm Silastic (Dow Corning) catheter with an attached subcutaneous access port was positioned in the left main coronary artery. Six animals received five weekly infusions of Adriamycin (doxorubicin hydrochloride) (10 mg/wk), and 3 received saline solution. Hemodynamic studies were performed before insertion of the catheter and 2 weeks after completion of the infusions. In animals that received Adriamycin, rest ejection fraction declined from 0.54 ± 0.03 to 0.35 ± 0.03, cardiac output fell from 5.6 ± 0.6 to 3.9 ± 0.5 L/min, and left ventricular end-diastolic volume increased from 76 ± 9 to 99 ± 12 mL ($p < 0.05$). There was a small increase in right atrial pressure (2.7 ± 1 versus 5.7 ± 1 mm Hg) but no change in right ventricular ejection fraction (0.31 ± 0.04 versus 0.30 ± 0.03). In no animal did alopecia, weight loss, neutropenia, or anemia develop. Histological changes consistent with Adriamycin-induced cardiac toxicity were found in each dog. No significant hemodynamic or histological changes occurred in the control animals. Administration of Adriamycin into the left main coronary artery causes left ventricular dysfunction without resulting in systemic side effects or compromising right ventricular function. This animal model could be used to evaluate the effects of new possible therapy, such as cardiomyoplasty, on left ventricular failure.

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Experimental heart failure has been induced with a variety of techniques, but no simple and reliable animal model of chronic heart failure has been developed [1–3]. Adriamycin (doxorubicin hydrochloride) causes dose-related cardiac toxicity in many animals, including humans [4–6]. Congestive heart failure can be induced in experimental animals by repeated intravenous injections of Adriamycin, but this method is limited by the substantial toxicity that occurs when the drug is given systemically [7–10].

A technique has been developed for administering multiple-dose intracoronary Adriamycin, which minimizes the systemic effects and preserves the cardiac toxicity of the drug. This initial report outlines the technique and characterizes its hemodynamic effects in the dog.

Material and Methods

Nine adult mongrel dogs weighing 25 to 32 kg were used in this experiment. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

The animals were premedicated with atropine sulfate (0.5 mg intravenously) and anesthetized with sodium pentobarbital (20 mg/kg intravenously). Anesthesia was maintained after endotracheal intubation with 1% inhaled isoflurane delivered through a volume-controlled, humidified ventilator.

Operative Technique

A left thoracotomy was made through the fifth intercostal space. The pericardium was opened and suspended with sutures. The highest diagonal branch of the left anterior descending coronary artery was mobilized for a distance of 2 cm and then ligated distally. A Silastic (Dow Corning) catheter (Norport; Norfolk Medical Products, Skokie, IL) with an external diameter of 1.5 mm was threaded into the diagonal branch in a retrograde fashion until the tip was in the left main coronary artery. The catheter was secured to the epicardium with multiple nonabsorbable sutures, and the attached percutaneous access port was buried in the subcutaneous tissue over the posterior portion of the seventh rib.

Use and Care of the Catheter

All 9 animals underwent insertion of the intracoronary catheter. Six animals received weekly infusions of Adriamycin, and 3 animals served as controls by having infusions of saline solution through the catheter. The Adriamycin solution was composed of 10 mg of Adriamycin in 60 mL of 0.9% saline solution and was infused over a 1-hour period using a Harvard pump (model 975; Harvard Apparatus Co, South Natick, MA). Control ani-

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Table 1. Hemodynamic Variables Before and After Infusions of Adriamycin or Saline Solution

	Adriamycin		Saline	
Variable	Before	After	Before	After
LVEF	0.54 ± 0.03[a]	0.35 ± 0.03[a]	0.58 ± 0.05	0.56 ± 0.04
EDV (mL)	76 ± 9[b]	99 ± 12[b]	72 ± 9	74 ± 10
dP/dt (mm Hg/s)	2,710 ± 218[b]	2,037 ± 285[b]	2,912 ± 368	3,012 ± 410
CO (L/min)	5.6 ± 0.6[a]	3.9 ± 0.5[a]	5.4 ± 0.5	5.5 ± 0.5
HR (beats/min)	133 ± 2	129 ± 7	126 ± 8	122 ± 9
PCWP (mm Hg)	6.3 ± 1.4	11.3 ± 1.6	7.1 ± 1.4	7.2 ± 1.6
RVEF	0.31 ± 0.04	0.30 ± 0.03	0.36 ± 0.05	0.33 ± 0.07
RAP (mm Hg)	2.7 ± 1	5.7 ± 1	3.1 ± 1	2.9 ± 1.2

[a] Significance: $p < 0.01$, before versus after. [b] Significance: $p < 0.05$, before versus after.

CO = cardiac output; dP/dt = rate of rise of left ventricular pressure; EDV = end diastolic volume; HR = heart rate; LVEF = left ventricular ejection fraction; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RVEF = right ventricular ejection fraction.

mals received weekly infusions of 60 mL of 0.9% normal saline solution. After each infusion and at least three times weekly, the catheters were flushed with 2 mL of a heparin sodium solution (1,000 U/mL) to maintain patency.

Evaluation

A complete blood count, a multigated acquisition scan, and right and left heart catheterization were done to establish control values. The initial infusion was given just after placement of the intracoronary catheter, and infusions were repeated each week for a total of 5 weeks. A complete blood count was obtained just before each infusion. Repeat multigated acquisition scan and heart catheterization were done approximately 3 weeks after the last Adriamycin infusion.

The radionuclide scans were performed with a portable gamma camera (model 412359MC3; General Electric, London, England) after the animals were injected with 20 μCi of technetium 99. Right heart pressures and thermodilution cardiac output determinations were obtained with a Swan-Ganz catheter, and left heart pressures were measured through plastic catheters filled with saline solution and connected to disposable transducers. The animals were sacrificed after the final cardiac catheterization, and biopsy specimens were obtained from the right and left ventricles for histological examination by light microscopy. The hearts were weighed, and the ratio of heart weight to body weight was calculated.

Each animal served as its own control for hemodynamic studies. Preinfusion and postinfusion hemodynamic and laboratory values were analyzed using paired *t* tests. The data are presented as the mean ± the standard error of the mean. A *p* value less than 0.05 was considered significant.

Results

Morbidity and Mortality

There were no operative deaths. None of the catheters occluded in the first 5 weeks, but all of them were occluded within 8 weeks of insertion. There were no instances of wound infection or erosion of the percutaneous access port through the skin. All of the animals survived for 3 months and then were killed. Overt congestive heart failure requiring therapy with diuretics and digoxin occurred in only 1 animal.

Hemodynamics

Initial and final hemodynamic values are presented in Table 1. All animals had normal baseline cardiac function. Follow-up studies showed a significant decline in left ventricular ejection fraction, cardiac output, and rate of rise of left ventricular pressure and a significant increase in end-diastolic volume. There was no change in right ventricular ejection fraction. Consistent increases in pulmonary capillary wedge pressure and right atrial pressure were noted, but the changes were not significant. There was no increase in heart weight or the ratio of heart weight to body weight over normal values for dogs.

Systemic and Histological Effects

In none of the animals did alopecia, weight loss, or bone marrow depression develop. Mean white blood cell count before and after the last Adriamycin infusion was 9.7 ± 1.2 × 10^9/L (9,700 ± 1,200 μL) and 8.4 ± 1.3 × 10^9/L (8,400 ± 1,300 μL), respectively. Mean hemoglobin concentration was 128 ± 10 g/L (12.8 ± 1.0 g/dL) at the start and 118 ± 4 g/L (11.8 ± 0.4 g/dL) at the conclusion of the experiment.

Histological examination showed increased interstitial fibrosis or extensive cytoplasmic vacuolation in each animal, which was confined to the left ventricle. These changes are consistent with Adriamycin-induced toxicity. A representative histological slide is presented in Figure 1.

Control Animals

Three animals received infusion of saline solution rather than Adriamycin. No significant hemodynamic or histological effects occurred in these animals.

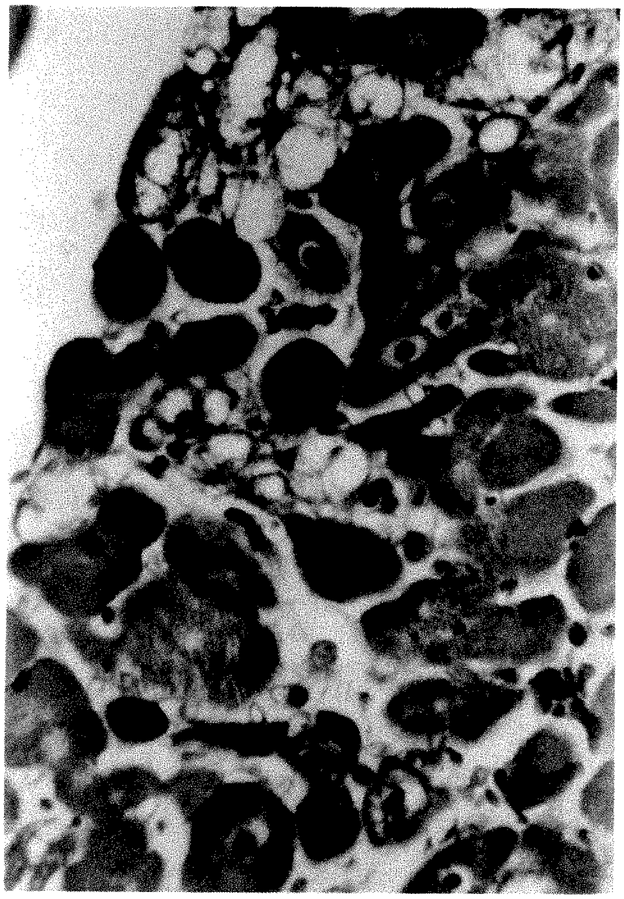

Fig 1. Extensive cytoplasmic and perinuclear vacuolation is evident. (Hematoxylin and eosin; ×150 before 30% reduction.)

Comment

Previous models of Adriamycin-induced cardiac toxicity have given the drug intravenously [3–7]. No significant systemic toxicity occurs when intracoronary Adriamycin is given in small doses, but left ventricular dysfunction still develops. The cardiac changes appear to be the result of the Adriamycin infusion rather than the presence of the intracoronary catheter, as infusion of Adriamycin resulted in heart failure, but infusion of saline solution through the catheter did not. In addition, none of the animals had evidence of major myocardial infarction at postmortem examination, a finding that demonstrates that the presence of the catheter did not cause thrombosis in the coronary arteries.

This model has several attractive features. The operative procedure is not difficult to perform, and operative morbidity and mortality are correspondingly low. Heart dysfunction develops, but it is limited to the left ventricle. Therefore, the animals do not have overt signs of congestive heart failure such as peripheral edema or ascites and are easier to manage than animals with biventricular heart failure. Finally, this model would be useful for evaluating the effects of therapeutic interventions on left ventricular function without the complicating variable of impaired right ventricular function.

This was a pilot study, and several questions remain to be answered. The dose–response relation between intracoronary Adriamycin and heart failure was not addressed. This protocol caused cardiac toxicity, but a different total dose or a different dosing interval might be more effective. The natural history of the heart failure induced by this technique is not known. Both stabilization of cardiac function and progression to profound failure are possibilities. The preliminary data presented here indicate that intracoronary Adriamycin might provide a simple and reliable animal model of left ventricular failure, but additional research will be necessary to fully characterize the model.

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We thank Dinean Samuel for preparing the manuscript, and Leslie Arelt for supervising the care of the experimental animals.

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Balloon Valvuloplasty After Pulmonary Valvotomy for Babies With Pulmonary Atresia and Intact Ventricular Septum

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During a 2½-year period, staged procedures of transventricular closed pulmonary valvotomy followed by balloon valvuloplasty were attempted in 12 babies with pulmonary atresia and an intact ventricular septum. All babies immediately underwent valvotomy when echocardiography revealed a tripartite right ventricle with adequate inflow and outflow dimensions and without sinusoidal–coronary arterial fistulas. After valvotomy, the overall mortality rate was 25% (3/12), but the only surgical death (1/12, 8%) was due to failure to establish continuity between the right ventricular cavity and the pulmonary trunk. The other 2 babies died of neonatal complications after successful valvotomy. Angiocardiography performed 5 to 18 months after valvotomy documented substantial growth of the right ventricular inflow and outflow dimensions in the 9 survivors. Twelve balloon dilation procedures were then performed in 7 babies. All except 1 achieved a significant drop in the right ventricular to left ventricular peak systolic pressure ratio (0.96 ± 0.40 to 0.56 ± 0.28; $p < 0.01$). Balloon valvuloplasty was not required in 1 baby and failed in the other, who then underwent successful right ventricular outflow tract reconstruction. After these staged procedures, follow-up at 1 month to 20 months (mean follow-up, 14.8 months) revealed resting cyanosis in 3 babies, which was related to severe residual infundibular stenosis (55 mm Hg) in 1 and a subnormal tricuspid valve annulus in 2. The remaining 5 babies (including 1 who required no valvuloplasty) were active and pink (saturation > 97%) and had a mean Doppler estimated gradient of 19 mm Hg (range, 8 to 36 mm Hg) across the pulmonary valve. Our results suggest that for babies with pulmonary atresia and intact ventricular septum, if echocardiography reveals an adequate tripartite right ventricle free from sinusoidal–coronary arterial fistulas, transventricular closed pulmonary valvotomy followed by balloon valvuloplasty is a simple biventricular staged repair with an acceptable outcome.

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In the management of pulmonary atresia with intact ventricular septum, the establishment of free continuity between the hypoplastic right ventricle and the pulmonary trunk is mandatory for the growth of the ventricular cavity [1–3]. Controversies exist as to the best approach to relieve the outflow tract obstruction. Transventricular closed valvotomy has been advocated for its simplicity [4, 5], but valvotomy through the pulmonary trunk without cardiopulmonary bypass [6] or patch reconstruction of the right ventricular outflow tract is favored by others as the primary procedure [7]. The introduction of balloon valvuloplasty provides a nonsurgical option to alleviate the ventricular outflow obstruction related to residual stenosis after previous valvotomy [8]. However, none of these decompressive procedures would be appropriate for managing babies who have a diminutive right ventricle incapable of supporting the pulmonary circulation independently or who have major sinusoidal–coronary arterial communications.

Advancements in technology have also greatly facilitated the treatment of this group of sick babies. High-resolution echocardiography allows accurate preoperative diagnosis and assessment of the morphology of the hypoplastic right ventricle and other associated anomalies, including major sinusoidal–coronary arterial fistulas [9]. The noninvasive investigation can also precisely measure the diameters of the tricuspid valve annulus, right ventricular infundibulum, and pulmonary trunk [9], all of which are important determinants of the choice of surgical approach and the prognosis for each patient [1–3]. The floppy, high-torque guidewires and low-profile balloon catheters now available have made it possible to cross and dilate residual stenotic valves in small babies [8].

Hence, over the past years, we have evolved a policy of performing transventricular closed pulmonary valvotomy for neonates with pulmonary atresia if echocardiography reveals a tripartite right ventricle with adequate diameters of the tricuspid valve annulus [3, 9], right ventricular infundibulum [10], and pulmonary trunk but without

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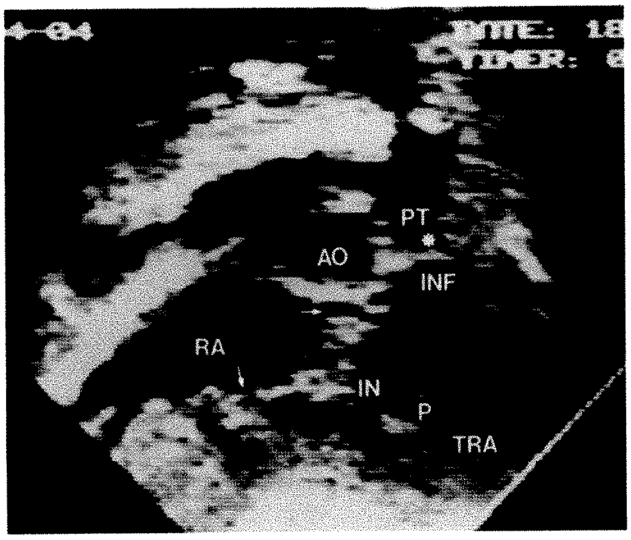

Fig 1. Subcostal echocardiographic view of the right ventricular outflow tract showing pulmonary valve atresia (*) and an adequate tripartite right ventricle. The inlet (IN), *trabecular* (TRA) *(beyond the insertion of the papillary muscle* [P] *of the tricuspid valve), and infundibular* (INF) *components of the ventricle are clearly depicted with relatively good inflow and outflow dimensions. This ventricle was judged capable of supporting the pulmonary circulation independently.* (AO = *aorta;* PT = *pulmonary trunk;* RA = *right atrium;* arrows = *tricuspid valve annulus.)*

major sinusoidal–coronary arterial fistulas. Whenever possible, we have avoided early cardiac catheterization of these sick, cyanotic neonates but have carried out that investigation with balloon valvuloplasty in early infancy to abolish any residual gradient across the right ventricular outflow tract. In this study, we review our 2½-year experience with this approach.

Material and Methods

Fourteen consecutive neonates with pulmonary atresia and intact ventricular septum who all had severe cyanosis after birth (mean age, 4 days) were admitted to the Department of Paediatrics in our institution between January 1988 and June 1990. Their diagnoses were confirmed by cross-sectional echocardiography with pulsed and continuous-wave Doppler flow studies [9]. The inlet, trabecular, and infundibular components of the hypoplastic right ventricles were then systematically evaluated, and the coronary arterial anatomy was carefully scrutinized using ultrasound investigation.

Twelve babies had a tripartite right ventricle (Fig 1) with adequate diameters of the tricuspid valve annulus (range, 1.1 to 2.0 cm; mean, 1.4 cm), the right ventricular infundibulum (range, 0.40 to 0.80 cm; mean, 0.54 cm), and the pulmonary trunk (range, 0.70 to 1.10 cm; mean, 0.80 cm) and without any evidence of sinusoidal–coronary arterial fistulas. They underwent transventricular closed pulmonary valvotomy after the echocardiographic examination. The prospective second stage of the approach consisting of cardiac catheterization with balloon valvuloplasty was performed after valvotomy.

The other 2 babies had a small tricuspid valve annulus (0.78 and 0.87 cm), an obliterated trabecular portion of the right ventricle, and a narrowed infundibulum (0.22 and 0.32 cm) (Fig 2). They had a systemic–pulmonary artery shunt operation only and are excluded from this review. Both underwent neonatal catheterization and angiography, which verified the right ventricular morphology as depicted by the echocardiogram and excluded sinusoidal–coronary arterial communications. They are awaiting a Fontan operation (univentricular repair).

Transventricular Closed Pulmonary Valvotomy

Transventricular closed pulmonary valvotomy was performed according to the technique described by Brock [11] and Sellors [12]. After a median sternal incision, the diaphragmlike pulmonary valve was split open by a pair of mosquito forceps introduced through a small stab incision in the right ventricular outflow tract. A Hegar's dilator, ranging from 4 to 6 mm in diameter, was then gently pushed through the ventriculopulmonary junction. Depending on the arterial saturation achieved, the preoperative infusion of prostaglandin E_2 was stopped at a variable period of 1 day to 5 days after valvotomy.

Cardiac Catheterization With Balloon Valvuloplasty

Cardiac catheterization was performed on all survivors under general anesthesia 5 to 18 months (mean period, 11.7 months) after valvotomy. Balloon valvuloplasty was attempted in all babies who had residual outflow tract obstruction with a right ventricular systolic pressure of 40 mm Hg or greater. A 5-mm balloon 2 cm long was required in 3 babies for initial dilation of an extremely narrow opening of the pulmonary valve. However, the ultimate balloon size (8 to 13 mm) chosen for all babies was 100% to 120% of the maximal pulmonary valve annulus measured from the right ventriculogram. In 4 infants, cardiac catheterization was repeated during the course of follow-up, and 2 of them underwent a second balloon dilation procedure. Hemodynamic data were recorded, and a biplane (anteroposterior with lateral) right ventriculogram was obtained before and after the interventional procedure. The right ventricular to left ventricular systolic pressure ratio was used as a better hemodynamic index of the severity of right ventricular hypertension and pulmonary stenosis. The ratio before valvuloplasty was compared with the hemodynamic data immediately after valvuloplasty or after the second interventional procedure.

Right Ventricular Inflow and Outflow Dimensions

As suggested by Bull and colleagues [13], we assessed the size of the right ventricle based on the tripartite classification by measuring the diameter of the tricuspid valve. In addition, we also measured the diameters of the right ventricular infundibulum and the pulmonary trunk and documented the growth of the hypoplastic right ventricle by serially measuring these anatomical structures. We [9] have previously demonstrated that these dimensions as retrieved from cross-sectional echocardiograms correlate well with the angiographic measurements. Hence, the preoperative right ventricular inflow and outflow dimen-

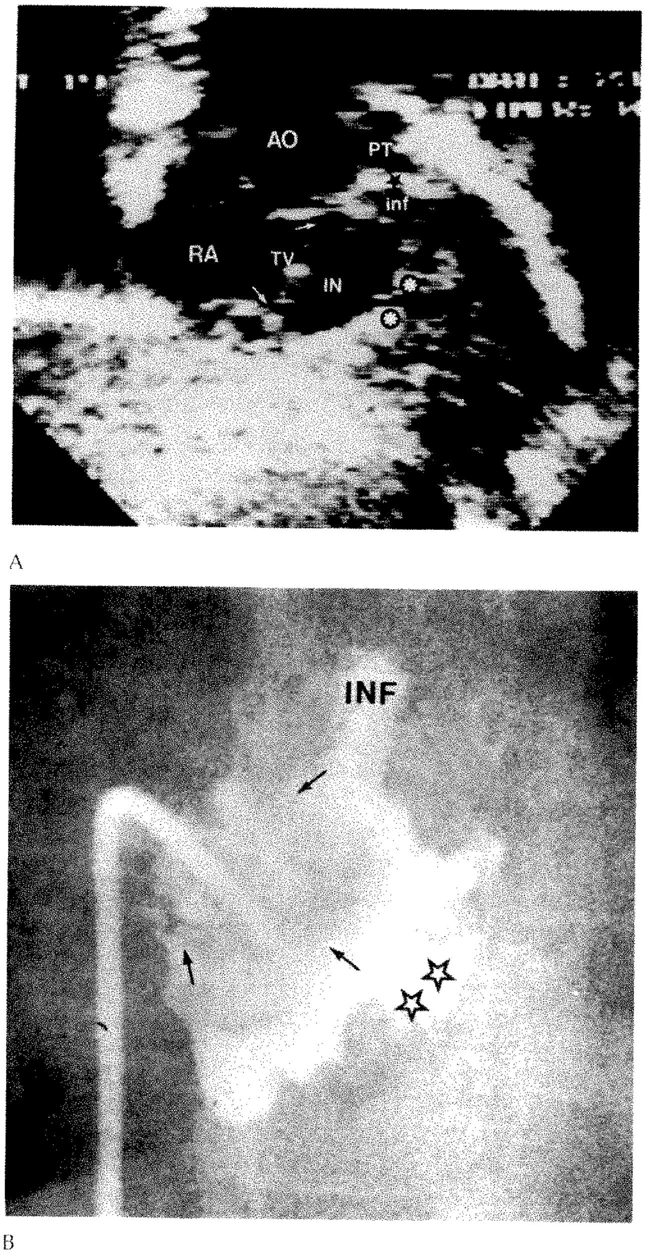

*Fig 2. Echocardiogram and angiogram from a baby with an obliterated trabecular component and narrowed infundibulum of the right ventricle. Both the ventricular cavity and its outflow were judged too small to support the pulmonary circulation independently. (A) Subcostal echocardiographic view showing a small ventricular cavity with the trabecular component obliterated by muscular hypertrophy (**). The infundibulum (*INF*) *is also very narrow compared with that in Figure 1. (B) Angiogram verifying the obliterated trabecular component of the right ventricle (☆☆) with a narrow infundibulum* (INF) *(0.32 cm).* (TV = *tricuspia valve;* arrows = *tricuspid valve annulus; other abbreviations are the same as in Figure 1.)*

sions of all survivors, which were obtained from the four-chamber and high precordial short-axis views of the neonatal echocardiogram, respectively, were compared with the measurements from the latest right ventriculogram available. The dimensions at the neonatal period were also compared between survivors and nonsurvivors.

Postmortem Studies

The heart specimens from the nonsurvivors were systematically examined and compared with the preoperative echocardiographic findings. The coronary arterial anatomy was examined for sinusoidal–coronary arterial fistulas [14] that might have been missed by echocardiography.

Follow-up Studies

At the latest follow-up, clinical evidence of right heart failure was sought. A pulse oximeter recording and a continuous-wave Doppler flow study across the right ventricular outflow tract were performed.

Statistical Analysis

Statistical analysis was performed with the paired Student's *t* test and Wilcoxon rank sum test where applicable. Statistical significance was assumed at the 5% level.

Results

Transventricular Closed Pulmonary Valvotomy

There were 3 hospital deaths (25%). One baby died in the immediate postoperative period despite ongoing prostaglandin infusion. Fulminating necrotizing enterocolitis developed in another baby, who died 2 weeks after operation. A late death occurred in a baby maintained on peritoneal dialysis for 6 weeks after valvotomy. These latter 2 nonsurvivors achieved a postoperative arterial oxygen tension consistently higher than 40 mm Hg, a finding indicating that the valvotomy was successful. All 9 survivors remained cyanotic after the procedure with an arterial oxygen tension ranging from 38 to 64 mm Hg. Two with a high arterial oxygen tension between 59 and 64 mm Hg required ligation of the persistent arterial duct 1 week later because of uncontrolled heart failure and ventilator dependence. After ductal ligation, they were successfully weaned off the ventilator.

Cardiac Catheterization and Balloon Valvuloplasty

The right ventriculograms of the 9 survivors confirmed that they all had a tripartite right ventricle judged capable of supporting the pulmonary circulation. A total of 12 dilation procedures (including three in 3 babies who required an initial small-sized balloon dilation) were carried out in 7 babies (Table 1). All except 1 achieved a significant drop in the right ventricular to left ventricular peak systolic pressure ratio (from 0.96 ± 0.40 to 0.56 ± 0.28; $p < 0.01$) (Fig 3). In 1 baby, only a guidewire, not the balloon catheter, could pass through the pinhole opening created by the previous valvotomy. He underwent successful right ventricular outflow tract reconstruction. One baby had a low right ventricular pressure (<40 mm Hg) at catheterization and did not require balloon valvuloplasty.

Right Ventricular Inflow and Outflow Dimensions

The inflow and outflow dimensions measured before closed pulmonary valvotomy showed no significant dif-

Table 1. Balloon Dilation for Pulmonary Atresia After Previous Valvotomy

Patient No.	Age at Valvotomy (d)	Age at Cardiac Catheterization (mo)	Before Valvuloplasty RV	Before Valvuloplasty LV	Before Valvuloplasty RV/LV	After Valvuloplasty RV	After Valvuloplasty LV	After Valvuloplasty RV/LV
1	4	16	50	90	0.56	37	90	0.41
2	3	15	75	60	1.25	14	60	0.23
3	2	18	40	75	0.53	34	75	0.45
4	5	5	120	75	1.60			
		17				40	80	0.50
5	25	7	90	70	1.29			
		18				65	75	0.87
6	2	12	90	90	1.00	80	80	1.00
7	3	6	65	80	0.81	38	80	0.48
8	2	11	80	60	1.33	. . .[a]	. . .	. . .
9	10	15	24	100	0.24	. . .[b]	. . .	. . .

[a] Only a guidewire could pass through the stenotic pulmonary valve. [b] Balloon valvuloplasty was not required, as pressure in RV was low.
LV = left ventricle; RV = right ventricle.

ferences between survivors and nonsurvivors ($p > 0.05$). For the 9 survivors, the echocardiographic and angiographic measurements of the tricuspid annulus, right ventricular infundibulum, and pulmonary trunk were all expressed as circumferences of their respective anatomical structures, and the results are depicted in Figure 4. There was a significant increase in the right ventricular inflow and outflow dimensions ($p < 0.01$), a finding reflecting growth of the ventricular cavity after closed valvotomy. Of the three sets of measurements, the dimensions of the right ventricular infundibulum remained grossly below normal limits [16] before and after valvotomy (see Fig 4B). In 2 babies, the diameter of the tricuspid valve annulus fell below normal limits [15] after valvotomy (see Fig 4A).

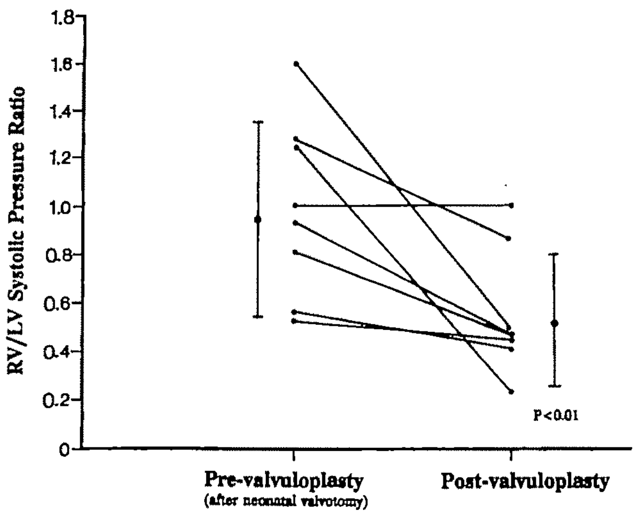

Fig 3. Hemodynamic data after balloon valvuloplasty for patients who had previous valvotomy. There is a significant reduction (p < 0.01) in the right ventricular (RV) to left ventricular (LV) systolic pressure ratio.

Postmortem Examination

All 3 babies who died underwent a postmortem examination. Each had a tripartite right ventricle with normal coronary arterial anatomy, which corresponded to the echocardiographic findings. All three heart specimens had complete fusion of the three leaflets of the pulmonary valve. In two, the anterior leaflet of the pulmonary valve was adequately split by the valvotomy procedure. The additional pathology of necrotizing enterocolitis and renal tubular necrosis as the causes of death for these 2 babies was also identified. In the third heart, an iatrogenic tract through the muscular infundibulum into the pulmonary trunk had been created by the valvotomy procedure. The fused pulmonary leaflets remained intact with the result that continuity between the ventricular cavity and the pulmonary trunk could not be established. This was the cause of the early death of this baby.

Follow-up Studies

The 8 survivors (the 1 who had right ventricular outflow reconstruction is not included), with or without balloon valvuloplasty, were followed up for 1 month to 20 months (mean follow-up, 14.8 months) after catheterization. At the latest follow-up, all were well and showed no evidence of heart failure. Continuous-wave Doppler study registered a pressure gradient of 36 mm Hg or less in all patients (range, 8 to 36 mm Hg; mean, 19 mm Hg) except 1, who had severe infundibular stenosis (55 mm Hg) despite propranolol hydrochloride therapy. This baby and 2 others whose measurements of tricuspid annulus diameter fell below normal limits (already mentioned [see Fig 4A]) but without a major residual gradient across the pulmonary valve (≤ 23 mm Hg) continue to remain cyanotic at rest (saturation, 80% to 92%). They are awaiting right ventricular outflow reconstruction with closure of the foramen ovale. The remaining 5 babies are active and pink (saturation >97%).

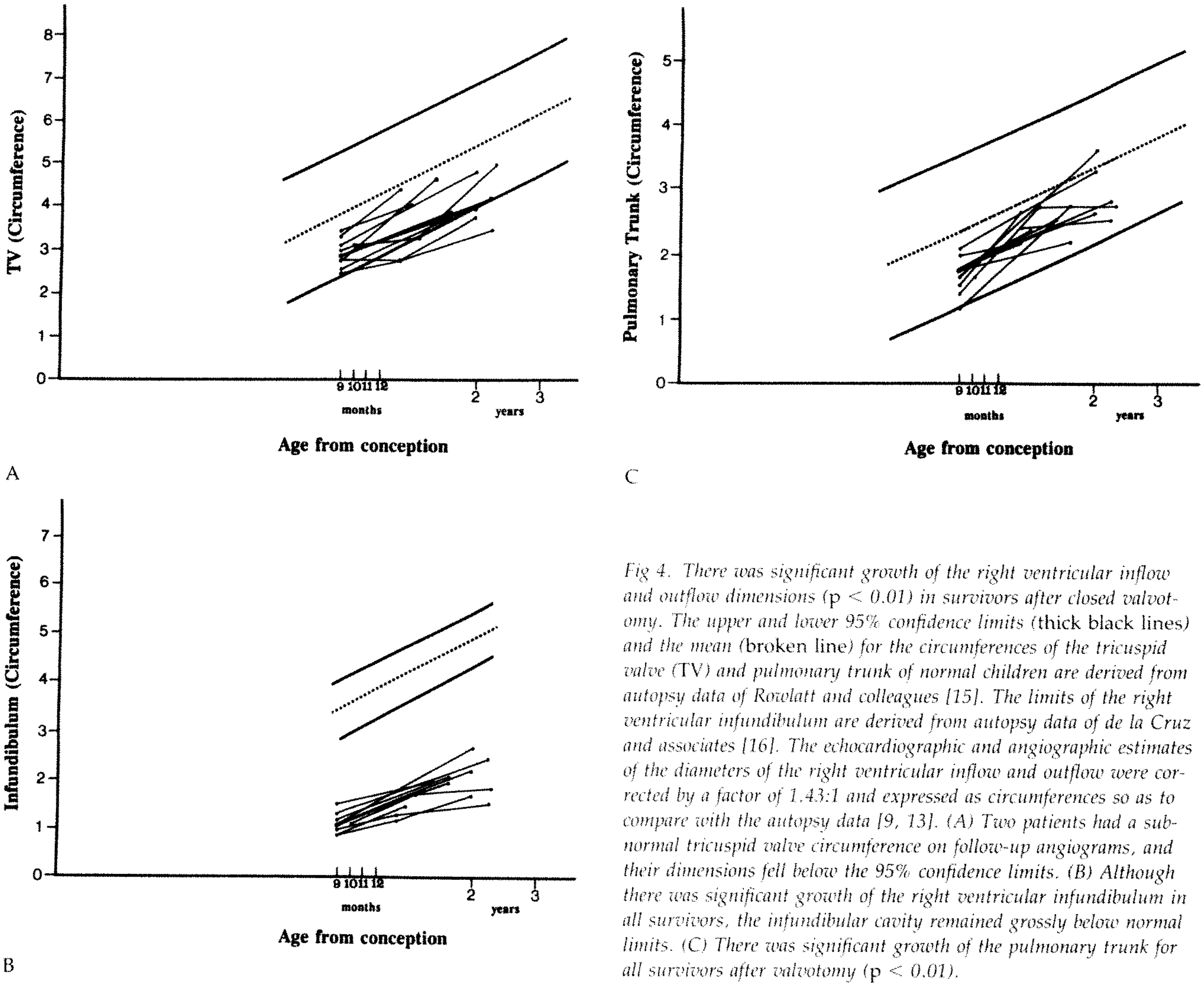

Fig 4. There was significant growth of the right ventricular inflow and outflow dimensions ($p < 0.01$) *in survivors after closed valvotomy. The upper and lower 95% confidence limits* (thick black lines) *and the mean* (broken line) *for the circumferences of the tricuspid valve* (TV) *and pulmonary trunk of normal children are derived from autopsy data of Rowlatt and colleagues [15]. The limits of the right ventricular infundibulum are derived from autopsy data of de la Cruz and associates [16]. The echocardiographic and angiographic estimates of the diameters of the right ventricular inflow and outflow were corrected by a factor of 1.43:1 and expressed as circumferences so as to compare with the autopsy data [9, 13]. (A) Two patients had a subnormal tricuspid valve circumference on follow-up angiograms, and their dimensions fell below the 95% confidence limits. (B) Although there was significant growth of the right ventricular infundibulum in all survivors, the infundibular cavity remained grossly below normal limits. (C) There was significant growth of the pulmonary trunk for all survivors after valvotomy* ($p < 0.01$).

Comment

The operative mortality rate for neonates with pulmonary atresia and intact ventricular septum is reported to range between 3.4% and 34% [4, 6], and in general remains relatively high. Because of this, various surgical procedures have been advocated for their initial management. Among the many approaches, transventricular closed pulmonary valvotomy is a simple, quick, and efficient operation to relieve the outflow tract obstruction provided the right ventricular anatomy is suitable [4, 5]. We have, therefore, adopted this surgical option for the initial treatment of babies with pulmonary atresia when they possess a tripartite right ventricle with an adequate tricuspid annulus and an adequate right ventricular infundibulum. In addition, we [9] use noninvasive echocardiography for our definitive diagnosis, and babies with suitable anatomy undergo valvotomy directly without previous catheterization. However, if echocardiography reveals a right ventricle with obliteration of one or two of its components, we perform cardiac catheterization to ascertain whether the ventricle is too small to support the pulmonary circulation (as in the 2 babies excluded from this study). Moreover, we want to rule out the presence of sinusoidal–coronary arterial fistulas, which tend to be associated with these ventricles with muscular atresia [1, 14]. In this present small series, no baby had major sinusoidal communications. This was purely coincidental and does not reflect any biased selection.

Our overall mortality (3/12, 25%) for valvotomy is comparable with that in other reports [4]. However, only 1 death was directly related to the operation (1/12, 8%), and it occurred because of failure to establish continuity between the ventricular cavity and the pulmonary trunk. The other 2 babies died of the neonatal complications necrotizing enterocolitis and renal tubular necrosis despite successful valvotomy. As for the 9 survivors, their right ventricular morphology as depicted by neonatal echocardiograms was later confirmed by angiography before the balloon dilation procedure. Based on these results, no neonate received inappropriate management because of an incorrect echocardiographic assessment. Moreover, the deaths after valvotomy were not related to the size of the right ventricle. This finding is supported by the absence of significant differences in the right ventricular inflow and outflow dimensions between survivors and nonsurvivors.

After valvotomy, we have routinely continued prostaglandin infusion to keep the arterial duct open until the baby's hemodynamics are stable with optimal arterial oxygenation (arterial oxygen tension > 35 mm Hg). In this way, we avoid performing a supplementary systemic–pulmonary artery shunt in babies who have a tripartite right ventricle capable of supporting the pulmonary circulation. This approach was also adopted by others who had found that a shunt was needed only infrequently [7]. After a successful valvotomy, additional shunting of blood into the pulmonary circulation might overload the left ventricle and cause uncontrolled heart failure. This occurred in 2 of our babies with a persistent arterial duct, which required ligation before they could be successfully weaned from the ventilator. Hence, we would reserve the creation of a systemic–pulmonary artery shunt for babies with a small right ventricle (with obliteration of one or two ventricular components) judged incapable of supporting the pulmonary circulation independently. We would plan a univentricular repair (Fontan operation) as the definitive management for this subset of patients.

Our results concur with those reported by Cobanoglu and associates [4] and suggest that valvotomy can at best only partially relieve the outflow obstruction in most babies. This is in contrast to the good long-term results described from other centers [5]. Universal to all the reported series, the survivors of valvotomy have significant growth of the hypoplastic right ventricle as reflected by the increase in size of the ventricular inflow and outflow dimensions. However, we noted the size of the right ventricular infundibulum in our babies to be grossly below normal [16] before and after the valvotomy procedure. Before any surgical intervention, the small infundibular cavity must represent an intrinsic property of the hypoplastic right ventricle of this complex cardiac anomaly. Although there is no existing guideline as to what constitutes an adequate infundibular size [12], we have arbitrarily chosen a diameter of greater than 3.2 mm on echocardiograms as the acceptable ventricular outlet for a right ventricle–dependent pulmonary circulation. This judgment is supported by the satisfactory survival rate of our babies after valvotomy (75%). Of concern is the failure to achieve a relatively normal size of the infundibulum after the surgical procedure. This is perhaps related to the substantial residual pulmonary valve stenosis seen in most of our survivors. It will be important to document whether the infundibular cavity grows further after adequate relief of this residual valvular stenosis.

To relieve the residual outflow tract obstruction after valvotomy, balloon valvuloplasty is an efficient nonsurgical alternative. The procedure was carried out smoothly in all but 1 of our infants requiring valvuloplasty after valvotomy. The growth of the right ventricular cavity after valvotomy probably contributes to the ease of crossing the stenotic valve by the catheters and minimizes the likelihood of rupturing the right ventricular infundibulum.

It is unlikely that valvotomy followed by balloon valvuloplasty can alleviate all the symptoms and hemodynamic disturbances of this cardiac malformation complex. Thus it is not surprising that at the latest follow-up, cyanosis at rest was still present in 3 babies who had either severe infundibular stenosis despite propranolol therapy (n = 1) or a subnormal tricuspid annulus diameter (perhaps reflecting suboptimal growth of the right ventricle) (n = 2). Cardiopulmonary bypass with reconstruction of the right ventricular outflow tract and closure of the foramen ovale would relieve any residual outflow obstruction and further improve the filling and growth of the right ventricular cavity. This must be the ultimate treatment for these 3 patients whose ventricle is considered capable of supporting the pulmonary circulation. As for babies with a diminutive right ventricle with or without sinusoidal–coronary arterial fistulas, an initial shunt operation followed by a univentricular repair (Fontan procedure) is the appropriate form of treatment. However, for neonates who have echocardiographic evidence of a tripartite right ventricle with adequate inflow and outflow dimensions and free from any sinusoidal–coronary arterial fistulas, the policy of closed pulmonary valvotomy followed by cardiac catheterization and balloon valvuloplasty in early infancy represents a simple biventricular staged repair with acceptable results.

We gratefully acknowledge the secretarial support of Miss Doris Chow and the invaluable assistance of Dr Peter Lo in the statistical analysis.

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REVIEW OF RECENT BOOKS

Surgical Revascularization of the Heart: The Internal Thoracic Arteries

By George E. Green, MD, Rani N. Singh, MD, and
J. A. Sosa, MD
New York, Igaku-Shoin Medical Publishers, 1991
219 pp, illustrated, $71.50

Reviewed by George J. Kontos, Jr, MD

Both cardiothoracic surgeons and cardiologists will benefit from the information in this book. Moreover, much of the information is directed toward practical clinical techniques.

This book begins with a brief history of coronary artery surgery and the emerging role of the internal thoracic artery (ITA) graft. The book presents the pathology of the ITA in great detail while attempting to answer the long-standing question of why the ITA is so privileged in regard to freedom from arterial disease when compared with other arteries of similar size.

Discussion of preoperative and postoperative evaluation of the ITA is particularly noteworthy and probably will prove most useful in the angiographic evaluation of patients having coronary reoperations. Although the authors emphasize use of an operating microscope, they have included extensive chapters on the technique of coronary artery bypass grafting employing the ITA (single ITA, bilateral ITA, and free graft) along with beautiful illustrations. Unlike all other chapters in this book, the chapter discussing postoperative morbidity after use of the ITA (postoperative bleeding, pulmonary complications, and sternal/ mediastinal wound infection) is much less comprehensive.

Overall, the text is well organized and particularly informative, with clinical examples and clear illustrations used in a complimentary fashion. This well-written book provides an excellent resource for surgeons and cardiologists in training, all cardiac surgeons performing coronary artery bypass operations, and interventional cardiologists.

San Antonio, Texas

A Surgical Technique That Preserves Human Saphenous Vein Functional Integrity

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We investigated the effect of a novel surgical preparative technique for human saphenous vein by using the concentration of adenosine triphosphate and the adenosine triphosphate/diphosphate ratio to quantify medial integrity and by using stimulated rates of prostacyclin production to quantify endothelial function. Freshly isolated vein had an adenosine triphosphate concentration of 358 ± 54 nmol $\cdot$ g^{-1} wet weight and an adenosine triphosphate/diphosphate ratio of 2.89 ± 0.13 (n = 12); it produced prostacyclin in response to fluid shear at a rate of 14.3 ± 2.0 pg $\cdot$ min^{-1} $\cdot$ mg^{-1} wet weight (n = 12). Surgically prepared vein obtained on completion of the last proximal anastomosis had been distended with the patient's own arterial pressure using a side-arm connected to the aortic cannula. This vein had an adenosine triphosphate concentration of 413 ± 70 nmol $\cdot$ g^{-1} wet weight and an adenosine triphosphate/diphosphate ratio of 2.74 ± 0.44 (n = 11), and it produced prostacyclin at a rate of 13.1 ± 0.2 pg $\cdot$ min^{-1} $\cdot$ mg^{-1} wet weight (n = 12). All values were indistinguishable from those in freshly isolated vein. The results demonstrate that this simple technique for distention at arterial pressure preserved medial and endothelial function.

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Autologous saphenous vein remains a widely used conduit for coronary artery bypass grafting despite its lesser long-term patency than the internal mammary artery [1–5]. Damage to the endothelium is associated with platelet and leukocyte adhesion and early graft thrombosis [3, 6]. Platelet-dependent phenomena such as organization of mural thrombus or release of mitogens may also trigger myointimal hyperplasia, the principal cause of late graft failure. Damage to vein graft media is also associated with leukocyte infiltration, another mechanism that may stimulate smooth muscle cell division by the action of macrophage-derived growth factors [7, 8]. Despite the lack of a controlled clinical trial, there is therefore a clear case for avoiding incidental endothelial and medial injury during surgical preparation.

Morphological and biochemical studies have shown that injury results from direct mechanical trauma and high-pressure luminal distention [9–13], whereas the nature of storage solutions and time of storage had less consistent effects [10, 13]. Moreover, surgical preparative injury can be minimized by reducing mechanical trauma and avoiding overdistention. A number of procedures have been developed to achieve these objectives [7, 9–12], among which we have proposed the use of a surgical technique employing first proximal anastomosis of the vein to the aorta before establishment of cardiopulmonary bypass, and distention with the pressure transmitted from the aorta [14]. This procedure, however, introduced substantial changes to the commonly used practice of first distal vein to coronary anastomosis. To simplify the overall procedure, we describe here a modification of the technique using first distal anastomosis and show that this also preserves endothelial and medial functional integrity.

Patients and Methods

Veins were obtained from 24 patients (18 men, aged 56 ± 5 years) who were undergoing a coronary artery bypass graft operation. Patients known to have received any nonsteroidal antiinflammatory drugs in the 2 weeks before the operation were excluded. Premedication, anesthesia, and heparinization were performed as detailed previously [10].

A segment of vein (approximately 1 to 2 cm), referred to as freshly isolated, was taken from the lower portion of the long saphenous vein as quickly as possible after the first incision was made. The vein was touched as little as possible, and dissection was kept to a minimum necessary to free the vein from surrounding tissue. Within 2 to 5 seconds of resection the segment was put either into liquid nitrogen or into Krebs-Ringer-bicarbonate HEPES (KRBH) buffer as detailed previously [10, 13]. The remaining vein was then dissected free of surrounding tissue, and all side branches were secured with 4-0 silk ligature. The vein was tied to a Tibbs cannula and then connected to the side-arm of the arterial cannula previously inserted into the ascending aorta. Before cardiopulmonary bypass was established the vein was perfused so as to distend it with the pressure transmitted from the aorta through the cannula (Fig 1). The vein was then disconnected and cut

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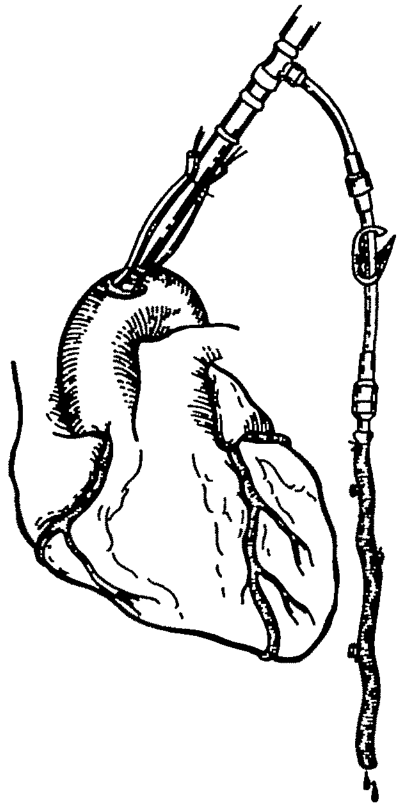

Fig 1. The saphenous vein is connected to the aortic cannula side-arm and distended by perfusion.

to an appropriate length for a particular aortocoronary graft and stored in 50 mL of the patient's heparinized arterial blood at room temperature.

The distal anastomosis was then performed after establishment of cardiopulmonary bypass, aortic cross-clamping, and cardioplegic arrest. After coronary reperfusion the proximal end of the graft was reconnected to the aortic cannula side-arm and redistended to establish orientation, avoiding kinking and allowing it to be cut precisely to the required length (Fig 2). After the graft was cut, the proximal anastomosis was performed and the surplus surgically prepared vein was used, in the case of the last graft, for biochemical analysis. A sample was put into either liquid nitrogen or KRBH buffer and taken from the operating theater to the laboratory. Segments (1 to 2 cm in length) of vein frozen in liquid nitrogen were processed for measurement of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate, and hypoxanthine concentration by high-pressure liquid chromatography [10]. Using separate 1-cm samples of vein taken into KRBH buffer, measurement of spontaneous rates of prostacyclin production (over a 30-minute incubation at 37°C) were performed as described previously [13]. The rings were then divided into three equal smaller rings and subjected to fluid shear by vortex mixing for 30 seconds followed by incubation at 37°C for a further 2 minutes. The vein was then removed and indomethacin (final concentration, 33.3 $\mu g \cdot mL^{-1}$) was added to inhibit further prostacyclin production. The prostacyclin released into the incubation media was quantified as 6-keto prostaglandin $F_{1\alpha}$ by radioimmunoassay [13].

Values are given throughout as mean ± standard error of the mean. Groups were compared by the Student's *t* test using unpaired values.

Results

Freshly isolated vein had an ATP concentration of 358 $nmol \cdot g^{-1}$ wet weight and an ATP/ADP ratio of 2.89 (Table 1). Sample excess of surgically prepared vein taken at the time the last proximal anastomosis was completed had an indistinguishable ATP concentration of 413 $nmol \cdot g^{-1}$ wet weight and an ATP/ADP ratio of 2.74 (see Table 1). The concentrations of adenosine monophosphate and hypoxanthine were also the same in freshly isolated and surgically prepared vein (see Table 1).

The rate of spontaneous prostacyclin production from freshly isolated vein was 2.0 $pg \cdot min^{-1} \cdot mg^{-1}$ wet weight, and this was stimulated to 14.3 $pg \cdot min^{-1} \cdot mg^{-1}$ wet weight by fluid shear resulting from vortex mixing (Table 2). Surgically prepared vein had a similar rate of spontaneous prostacyclin production of 1.9 $pg \cdot min^{-1} \cdot mg^{-1}$ wet weight, which was stimulated to 13.1 $pg \cdot min^{-1} \cdot mg^{-1}$ wet weight by fluid shear (see Table 2). This stimulated rate was slightly but not significantly different from that of freshly isolated vein.

Comment

Several techniques have been described that reduce damage to human saphenous vein caused during surgical

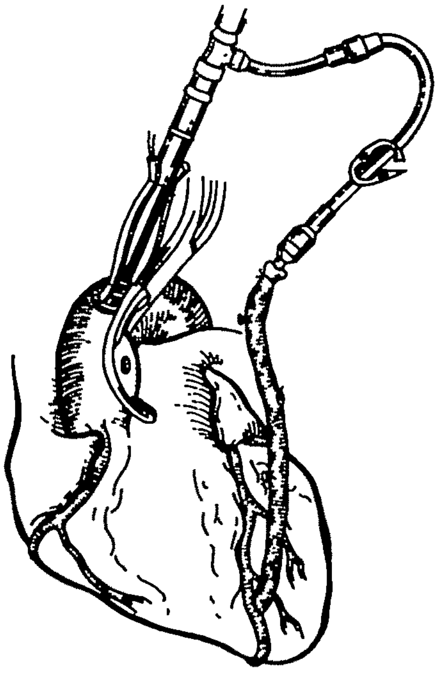

Fig 2. On completion of the distal anastomosis the vein is reconnected to the aortic cannula side-arm and redistended to establish orientation before performance of the proximal anastomosis.

Table 1. Purine Metabolite Concentrations in Freshly Isolated and Surgically Prepared Veins

	Metabolite Concentration (nmol · g^{-1} wet weight)				
Condition	ATP	ADP	AMP	Hypoxanthine	ATP/ADP Ratio
Freshly isolated (n = 12)	358 ± 54	117 ± 12	26 ± 6	47 ± 9	2.89 ± 0.13
Surgically prepared (n = 11)	413 ± 70	145 ± 20	24 ± 5	34 ± 15	2.74 ± 0.44

ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate.

preparation for coronary artery bypass grafting [7, 9, 11, 14]. Damage has been assessed by subjective or semiquantitative histological examination. More recently, we introduced the use of measurements of ATP concentration and ATP/ADP ratio as quantitative biochemical markers of medial cell integrity [10]. Likewise, we have shown that prostacyclin production stimulated by fluid shear is endothelium-dependent in human saphenous vein and its rate correlates closely with a degree of endothelial coverage determined by morphometry [13]. Using these quantitative markers, we established that direct mechanical trauma is the main cause of endothelial injury during surgical preparation [13], and excessive luminal distention is the principal cause of medial injury [10].

Storage in various solutions including blood physiological saline or 154 mmol/L sodium chloride solution had little impact on functional integrity [13]. Thus the optimized methods of preparation that have been described previously have sought to limit incidental mechanical trauma and distention pressure. Mechanical injury has been reduced by dissection with minimal touching [15] of the vein, whereas distention pressure has been limited either by including a manometer [9] or by interposing a commercially available latex balloon device between the syringe and the vein to be distended [11]. It occurred to us, however, that a simple procedure for distending veins was to connect them to the patient's arterial blood supply. Consistent with this idea, we showed in a previous study that first proximal anastomosis of the vein to the aorta and distention with the patient's own arterial pressure led to minimal injury [14]. The method, however, required a switch from the more common surgical practice of making the vein to coronary anastomosis first. In this study, we therefore modified the technique by distending the vein with the pressure transmitted from a side-arm attached to the aortic cannula. After this, no other changes were introduced to the routine of first distal anastomosis. The pressure transmitted from the aortic cannula was found to be sufficient to distend the vein, reverse spasm, and check the competence of side-branch ligatures. After completion of the distal anastomosis, reconnection of individual vein segments to the aortic cannula side-arm to check for graft orientation and length has the additional potential benefit of immediately reperfusing poorly perfused areas of the heart. Indeed, when necessary, a side-arm with multiple ends as described by Kauten [16] has been used to perfuse several grafts at a time.

The involvement of the principal surgeon in checking side-branch ligatures and storing the vein may be seen as a drawback of the proposed technique. We believe that the experimental evidence that links surgical preparative injury to early graft occlusion [6] justifies this assignment of priorities. Otherwise, the technique described here can be adopted without need for radical change in surgical practice and has become a routine in our institutions over the last 2 years.

Table 2. Spontaneous and Stimulated Rates of Prostacyclin Production From Freshly Isolated and Surgically Prepared Veins

	Rate of Prostacyclin Production (pg · min^{-1} · mg^{-1} wet weight)	
Condition	Spontaneous	Stimulated by Fluid Shear
Freshly isolated (n = 12)	2.0 ± 0.4	14.3 ± 2.0
Surgically prepared (n = 12)	1.9 ± 0.2	13.1 ± 0.2

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Notice From the Southern Thoracic Surgical Association

The Thirty-ninth Annual Meeting of the Southern Thoracic Surgical Association will be held at the Saddlebrook Golf and Tennis Resort, Wesley Chapel (near Tampa), Florida, November 5–7, 1992. The Postgraduate Course will be held the morning of Thursday, November 5, 1992, and will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Members wishing to participate in the Scientific Program should submit an original abstract and one copy by May 15, 1992, to Walter H. Merrill, MD, Program Chairman, Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267. Abstracts must be submitted on the Southern Thoracic Surgical Association abstract form. These forms may be obtained from the Association's office or in the April issue of *The Annals of Thoracic Surgery*. Manuscripts of accepted papers must be submitted to *The Annals of Thoracic Surgery* prior to the 1992 meeting or to the Secretary-Treasurer at the opening of the Scientific Session.

Applications for membership should be completed by July 1, 1992, and forwarded to John P. Clarke, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267.

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Cardiomyoplasty Does Not Preclude Heart Transplantation

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Stimulated skeletal muscle grafts have been proposed to improve left ventricle function in patients with severe myocardial failure. In 1 particular case reported here, however, the postoperative functional improvement was only transient and disabling heart failure recurred after 9 months in spite of a vigorous latissimus muscle contraction. Heart transplantation was proposed to this patient and performed successfully. Technically, the key to heart removal depends on the retrograde dissection of the ventricular cavities, starting from the right atrioventricular groove. The intraoperative observations confirmed the viability of the latissimus dorsi muscle, inefficient on a highly dilated cardiomyopathy. Histopathological examination of the latissimus dorsi muscles showed that the transformation process of the stimulated muscle was good. Thus, severe cardiac dilatation seems to be one of the limitations of cardiomyoplasty. Cardiomyoplasty, when it fails, does not preclude heart transplantation. The histochemical studies confirm the electrophysiologic principle of cardiomyoplasty in humans.

(Ann Thorac Surg 1992;53:875–81)

In 1985, Carpentier and associates [1] reported the first cardiomyoplasty using the latissimus dorsi muscle (LDM) graft ever achieved in a human patient. Since then, and while experimental research is still continuing [2, 3], several teams have performed this dynamic cardiac assistance technique in humans [4–7]. Our experience of cardiomyoplasty in patients with severe and intractable heart failure started in 1989, and to date 12 patients have benefited from this technique using the LDM and the system of cardiomyostimulation developed by Medtronic (SP 1005 Cardiomyostimulator pulse train generator, SP 5528 intramuscular leads; Medtronic Inc, Maastricht, the Netherlands). In 1 particular case the postoperative functional improvement was only transient, and disabling heart failure recurred in the ninth month after operation despite the good functionality of the cardiomyoplasty performed. Heart transplantation was proposed to this patient and performed successfully.

We report the original observation of this patient and discuss the efficacy and limitations of cardiomyoplasty in advanced heart failure, as well as the cardiomyoplasty procedure and the surgical feasibility of cardiac transplantation after cardiomyoplasty and the structural modifications of the fibers of the stimulated LDM in humans.

Case Report

A 59-year-old man with dilated ischemic cardiomyopathy, New York Heart Association (NYHA) functional class IV, was selected for cardiomyoplasty in December 1989. His history began in 1973 with extensive anteroseptal myocardial infarction with residual angina. In 1982 the severity of the angina and the occurrence of dyspnea made it necessary to perform a coronary arteriography. There was no indication of myocardial revascularization. By the end of 1988, after an episode of acute pulmonary edema, NYHA class IV heart failure set in and, eventually, cardiac transplantation was proposed. The patient's name was registered in the waiting list of candidates for heart transplantation in February 1989.

After 9 months of waiting, the patient requested alternative therapeutics to heart transplantation. A new hemodynamic evaluation was performed in December 1989 (Table 1), revealing a dilated, overall hypokinetic left ventricle; contractility was present only in the laterobasal part of the left ventricle. The coronary artery anatomy precluded any coronary artery grafting. There was three-vessel disease: circumflex artery occlusion and not significant stenoses of the right coronary artery and of the left anterior descending artery. The distal runoff of the three vessels was very poor. There was neither pulmonary artery hypertension nor mitral valve insufficiency. Chest roentgenography (Fig 1) revealed moderate cardiomegaly (cardiothoracic ratio, 0.55). Cardiomyoplasty was decided on and then proposed to and accepted by the patient. Cardiomyoplasty was performed in this patient on January 9, 1990, according to the technique described by Carpentier, Chachques, and their associates [8, 9].

Dissection and Transposition of the Latissimus Dorsi Muscle

With the patient in the right lateral decubitus position, the left LDM was dissected free of its distal insertions and the

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Table 1. Data Preoperative, and 6-Month, After Cardiomyoplasty

Variable	Preoperative	Postoperative
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.02	1.78
Arteriovenous oxygen difference (mL/L)		
At rest	69.2	73.2
Exercise	94.6	102.8
Pulmonary capillary wedge pressure (mm Hg)		
At rest	9	29
Exercise	31	62
Mean pulmonary artery pressure (mm Hg)	19	35
LV end-diastolic pressure (mm Hg)	20	27
Arterial lactate level (mmol/L)		
At rest	1.15	1.15
Exercise	1.80	3.19
LV ejection fraction	0.30	0.17
LV end-systolic diameter (mm)	73	73
LV end-diastolic diameter (mm)	85	81

LV = left ventricular.

superior neurovascular bundle was identified and carefully preserved. Latissimus dorsi muscle flap hemostasis was completed by metallic surgical clips. At the end of the dissection, the muscle was delineated by clips. A 6-cm segment of the anterior portion of the second rib was then resected to allow transposition of the LDM into the thorax. To perform chronic muscular stimulation, two juxtaneural pacing electrodes (Medtronic SP 5528) were implanted in the proximal portion of the LDM. Electrophysiological tests (threshold, impedance) were performed. The LDM and attached leads were then transposed into the left pleural cavity. The muscle was fixed with four interrupted sutures to the intercostal muscles at the level of the second rib resection. To avoid left arm movement during electrostimulation, the latissimus dorsi humeral tendon was then severed at its most proximal part.

Cardiomyoplasty

The patient was then placed in the supine position and the heart was exposed through a median sternotomy incision. The technique of reinforcement was used and cardiopulmonary bypass was not required. The pericardium was dissected to be used later as a pericardial patch. The LDM graft was slipped behind the ventricles, along the left atrioventricular groove, and maintained by three stitches: one in the pericardium opposite the left atrium, one at the root of the inferior vena cava, and one at the lower edge of the right atrioventricular groove (Fig 2). Two intramyocardial sensing leads (Medtronic SP 5548) were implanted on the right ventricle wall. The muscle wrapping was then achieved, with the surface of the LDM covering the lateral, anterior, and diaphragmatic walls of the ventricle; the free edges of the LDM were sewn together with a continuous suture. The upper edge of this muscle wrapping was attached to the pulmonary annulus. The pericardial patch was attached to the free edge of the muscle wrapping and to the right edge of the pericardium, in order to cover the anterior wall of the right ventricle not covered by the LDM and maintain the muscle wrapping in place by securing it to the right edge of the pericardium (Fig 3). Muscle and cardiac leads were coupled with the cardiomyostimulator implanted in the epigastric wall.

This patient's LDM was of good quality, with low stimulation thresholds, allowing nearly complete covering of the ventricular cavities and interposition of a small pericardial patch. The whole duration of postoperative hospitalization was 26 days. Stimulation of the LDM was initiated 21 days after operation, ie, after the time needed for the development of muscle-to-myocardium adhesions. Muscle stimulation followed the usual protocol [4, 8]: progressive increase in the number of electrical impulses transmitted to the muscle made it possible, by transformation of the striated fibers within 2 months postoperatively, to obtain effective LDM contraction during every other ventricular systole (Fig 4). At this stage, the starting time of LDM stimulation was synchronized with the closure of the mitral valve, as shown by echocardiography. The use of metallic clips during muscle dissection also allowed a radiocinematographic study of the kinetics of the stimulated LDM.

After the second postoperative month (March 1990), the patient showed functional improvement from NYHA functional class IV to NYHA class II^{+}/III^{-}, without any clinical sign of cardiac failure, and was receiving therapy based on three drugs (furosemide, 80 mg/day; digoxin,

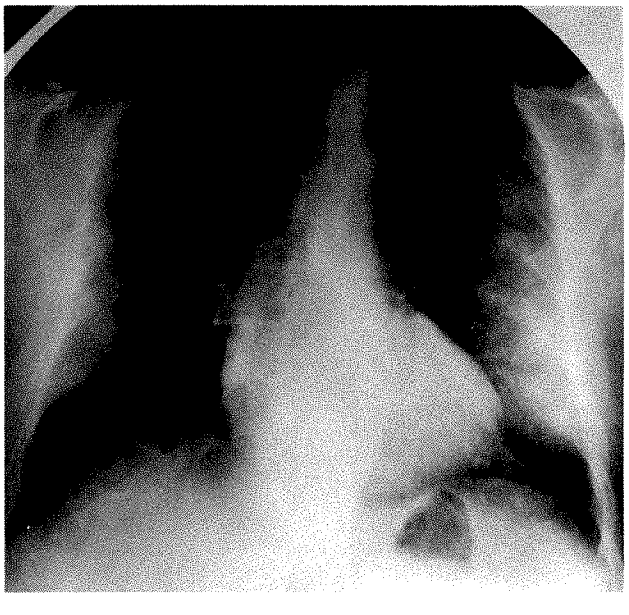


Fig 1. Preoperative chest roentgenogram.

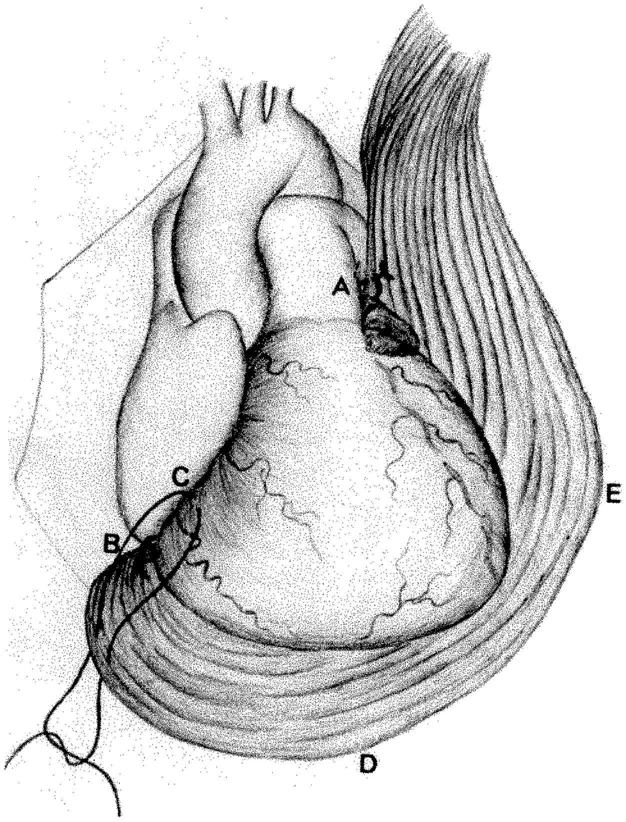


Fig 2. Surgical technique of ventricular cardiomyoplasty. Left latissimus dorsi muscle in mediastinal space is positioned behind the heart, and secured with three stitches: (A) in the pericardium opposite the left atrium, (B) at the root of the inferior vena cava, and (C) at the lower edge of the right atrioventricular groove. Points D and E are used as reference points.

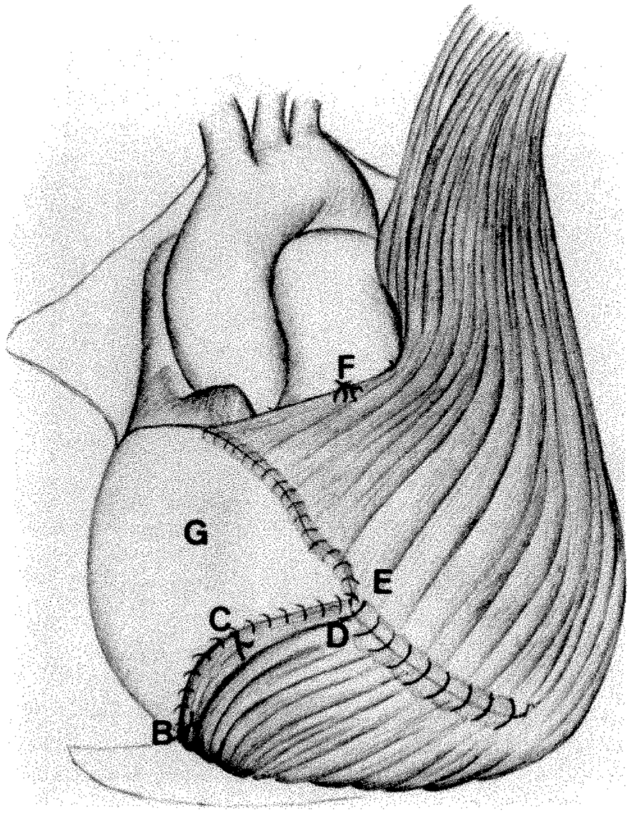


Fig 3. The muscle is wrapped onto the lateral and anterior wall of the ventricles. The clockwise wrapping is secured with the pulmonary annulus (F) and the pericardial patch (G). (Other points as in Figure 2.)

0.25 mg/day; isosorbide dinitrate, 60 mg/day). The chest roentgenogram showed the LDM graft and the position of the electrodes (Fig 5). However, invasive explorations performed 6 months postoperatively (July 1990) showed marked hemodynamic changes (see Table 1) in sharp contrast to the picture of functional improvement. Captopril, 50 mg/day, was added to his medication.

In August 1990, the patient had three episodes of acute pulmonary edema: two of these were secondary to ventricular arrhythmia, but the third one occurred in the hospital and no arrhythmia was recorded. Consequently, in view of the patient's functional and hemodynamic aggravation, it was decided to resort to cardiac transplantation, accepted by him and performed on September 7, 1990.

Heart Transplantation

Narcoanesthesia was performed with flunitrazepam and fentanyl. The patient's hemodynamic instability required nasotracheal tubing and the use of pancuronium. The use of curare precluded any dynamic study of the cardiomyoplasty during the procedure.

After median sternotomy, the retrosternal symphysis was gradually liberated; the pericardial patch covering the right atrium and the frontal wall of the right ventricle was dissected, so that the cleavage plane now ran between the LDM extending around the cardiac cavities and the anterior thoracic wall. The pericardial patch was opened lengthwise; the right atrium and the aorta were dissected and prepared for cannulation. The adhesions between the LDM graft, left lung, and left pleuropericardial leaf prevented any frontal approach for dissecting the ventricular cavities and the muscular wrapping. A posterior approach was used for removing the LDM graft from the pericardial sac; this dissection started first with the diaphragmatic wall from the level of the right atrioventricular groove and

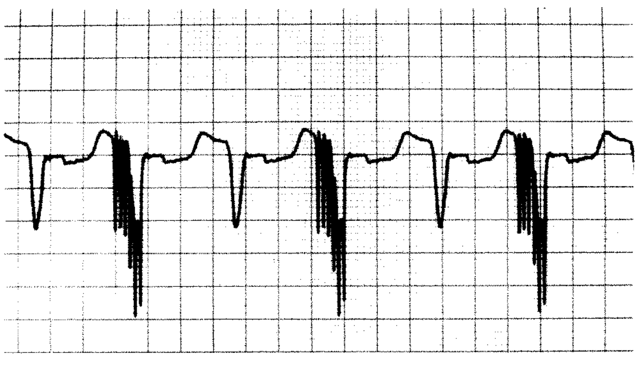


Fig 4. Postoperative electrocardiogram shows synchronous stimulation of latissimus dorsi muscle graft with an interval of 75 ms between the beginning of QRS and the train of six impulses (2:1).

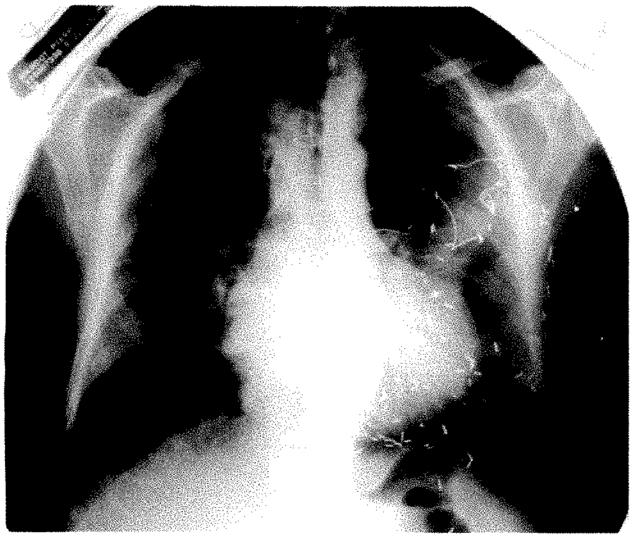


Fig 5. Postoperative chest roentgenogram shows a left paracardiac density produced by the latissimus dorsi muscle graft covered by radiopaque clips.

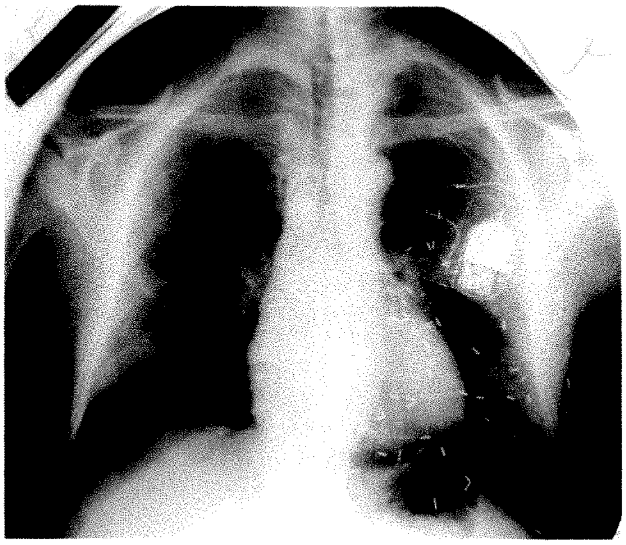


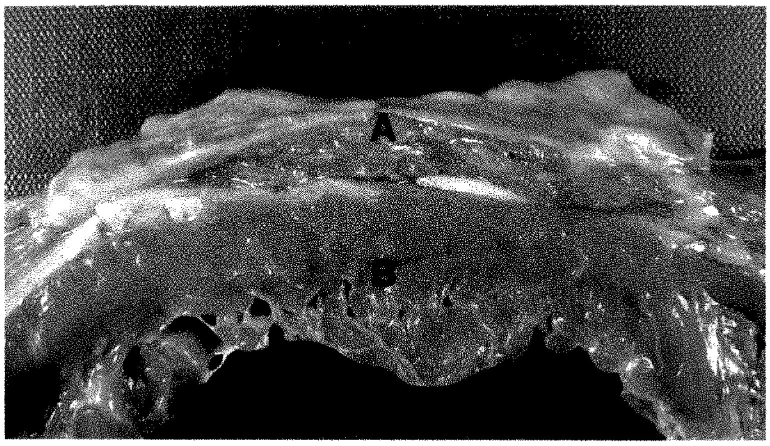
Fig 7. Posttransplantation chest roentgenogram. The latissimus dorsi muscle intrathoracic pedicle is retracted in the left axillary thoracic wall.

continued with the posterior wall from the left atrioventricular groove down to the apex of the left ventricle. Dissection was continued under extracorporeal circulation and after aortic clamping. The lateral wall of the left ventricle was liberated from bottom to top by gradual displacement of the ventricular cavities. Finally, the proximal portion of the LDM, lying transthoracically, could not be released from its pleuropulmonary adhesions and was cut flush with the pericardium while the left phrenic nerve was preserved. This very fleshy and highly vascularized muscle pedicle was unresectable. It was left in the thorax, along with the proximal ends of the muscle-stimulating leads. Cardiectomy was then performed, with the ventricle globes wrapped in the muscle graft. Four biopsies of the LDM were carried out, and the specimens were stored in liquid nitrogen. The LDM was alive, not fibrous, without any cleavage plane from the myocardium; its thickness was 10 to 15 mm (Fig 6).

The transplant was the heart of a 16-year-old, 1.8-m, 68-kg man who had died of cerebral hemorrhage. Once the vascular anastomoses were completed, the heart spontaneously resumed its activity, exhibiting adequate hemodynamics. At the end of the procedure, after closure of the sternotomy, the pulse generator and its electrodes were removed. Two biopsies of the right LDM were carried out. The patient had to be reoperated on 12 hours later because of hemorrhage. A cardiac pacemaker was implanted on the tenth day after operation because of impaired atrioventricular conduction. The total duration of hospitalization after transplantation was 45 days. The patient had a graft rejection episode 2 months after transplantation, which was successfully treated by corticosteroids. One year after transplantation, the patient was alive, at home, with adequate functional health and a good chest roentgenogram (Fig 7).

Histochemical studies (staining of the enzymes adeno-

Fig 6. Cross-section of the left ventricle. The latissimus dorsi muscle graft (A) is adherent to the myocardium (B).



sine triphosphatase and succinate dehydrogenase) carried out on biopsy specimens of the stimulated left LDM and of the nonstimulated right LDM confirmed the complete transformation of the glycolytic fibers into oxidative fibers after electrostimulation: the unstimulated muscle contained 70% glycolytic fibers and 30% oxidative fibers (Fig 8); after 8 months of electrostimulation the stimulated muscle contained oxidative fibers almost exclusively (Fig 9).

Comment

In the wake of Carpentier and Chachques [1], several teams have reported their experience with cardiomyoplasty in humans. Hagege and co-workers [10] reported 5 patients with hemodynamic and functional improvement of long-term duration averaging 8.4 months postoperatively. Moreira [11] reported 11 patients, 8 of whom had long-term improved condition averaging 11 months, and all 11 of whom had hemodynamic and functional improvement. In our own experience, of 12 patients with a mean follow-up of 10 ± 3 months, 8 have shown functional improvement with increased response to exercise [12].

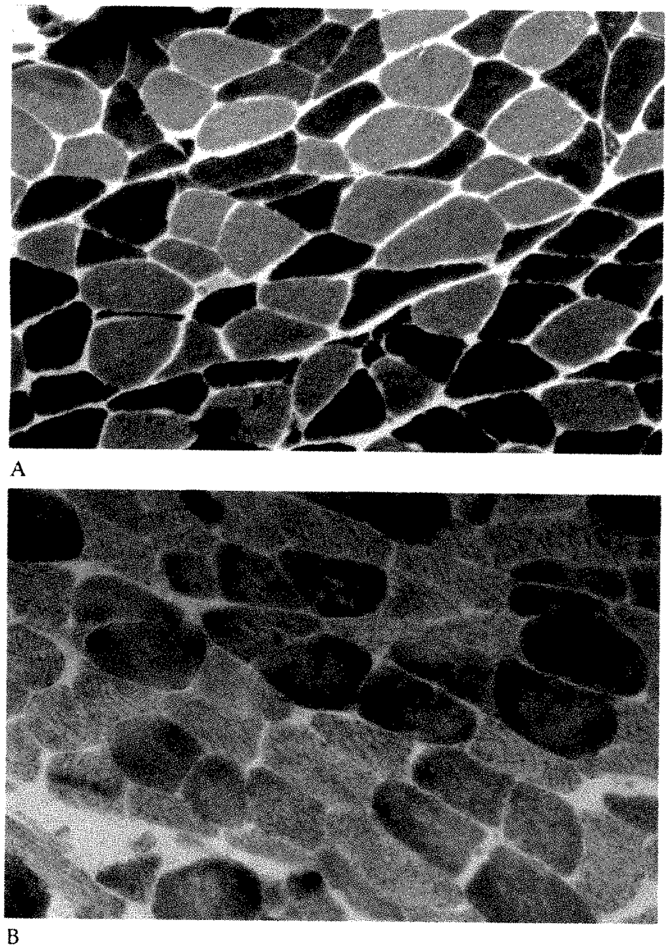


Fig 8. Histochemical muscular studies of nonstimulated control right latissimus dorsi muscle: (A) adenosine triphosphatase activity at pH 9.4; (B) succinate dehydrogenase activity. Dark stained fibers are type I, oxidative fatigue-resistant fibers (30%); light stained fibers are type II, glycolytic fatigue-sensitive fibers (60%).

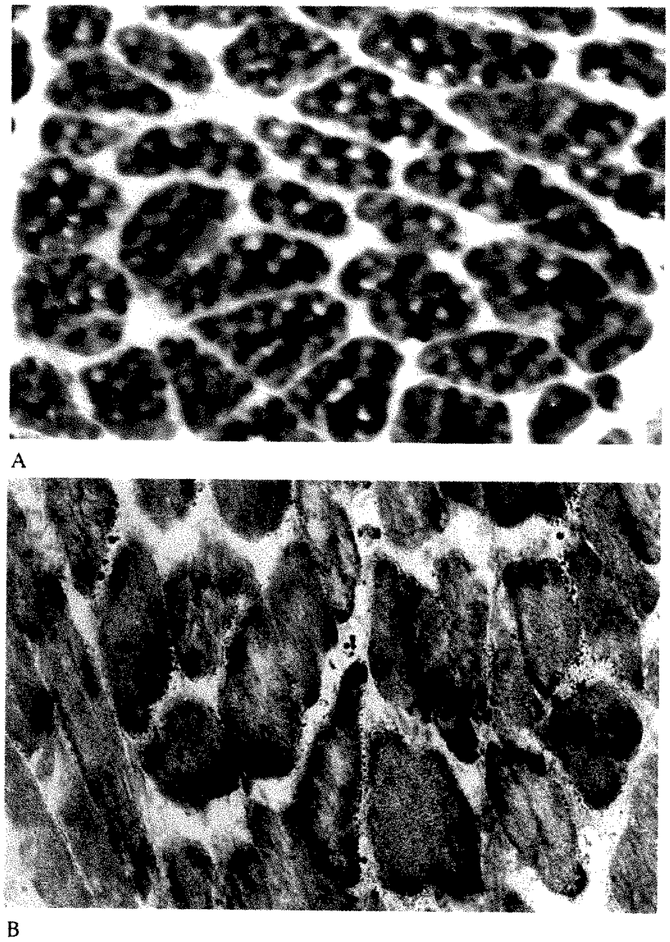


Fig 9. Histochemical muscular studies of stimulated left latissimus dorsi muscle: (A) adenosine triphosphatase activity at pH 9.4, (B) succinate dehydrogenase activity. Complete conversion to type I, oxidative fatigue-resistant fibers (dark stained fibers) is seen.

In this article, we report cardiac transplantation after previous cardiomyoplasty. Undeniably, this cardiomyoplasty was a failure, not in its principle but in its application. Indeed, in spite of a transient functional improvement, the cardiomyoplasty proved insufficient to stabilize and, therefore, unable to improve this patient's severe ischemic cardiomyopathy. His functional and hemodynamic status declined after 6 months although the stimulated LDM was functional, as confirmed by echography and radiocinema studies. Before cardiomyoplasty, this patient had a markedly impaired left ventricle (end-diastolic diameter, 85 mm). The same features were also present in 2 other patients in our series whose conditions were not improved after cardiomyoplasty. Retrospectively, in these patients, cardiomyoplasty was not indicated. As it seems, left ventricular end-diastolic diameter exceeding 80 mm and class II pulmonary artery hypertension constitute the present limitations for cardiomyoplasty indications [11].

The relationship between LDM thickness and left ventricle wall thickness, as well as the quality of the underlying left ventricle, probably control the efficacy of the cardiomyoplasty. One may imagine that the more dilated the left ventricle, the greater the gain in contractility brought by the LDM has to be, at the point of exceeding its physiological capabilities. Clinical results seem to be much better in Chagas' disease [11], or in idiopathic dilated cardiomyopathies where the ventricle wall is flexible and not hypertrophic [10], than in ischemic cardiomyopathies (as in our series) where a certain degree of myocardial fibrosis is present. Also, the worsening of the underlying cardiomyopathy may compromise later the efficacy of the cardiomyoplasty, as in Chagas' disease. However, the mechanism of action of the stimulated LDM on the left ventricle function remains uncertain. The basic concept consists in increasing left ventricle contractility, thereby aiming at improving left ventricle systolic function [5, 13], but the mechanism of action could be an effect on left ventricle diastolic function that improves ventricular compliance and increases myocardial extra capability.

On the other hand, in the case we report here, the failure of cardiomyoplasty may be secondary to a worsening of the underlying cardiomyopathy promoted by the occurrence of two episodes of arrhythmia. Only long-term studies will allow a final conclusion as to whether cardiomyoplasty is liable not only to improve a patient's clinical and hemodynamic condition but also to stabilize any underlying cardiomyopathy.

However, in case of cardiomyoplasty failure, cardiac transplantation remains possible and can be successfully achieved. Technically, the key to heart removal depends on the posterior dissection of the ventricular cavities, starting from the right atrioventricular groove. The interposition, during cardiomyoplasty, of a pericardial patch partially covering the right cavities facilitates the dissection of the right atrium and the aorta, and helps one find the dissection planes between the diaphragmatic pericardium and the ventricular cavities covered with the LDM graft. We chose not to remove the intrathoracic LDM pedicle, and we cut the LDM graft flush with the left pleurocardial leaf. After the procedure, this intrathoracic pedicle seemed to retract in contact with the left axillary thoracic wall; it was no longer visible on the posttransplantation thoracic roentgenogram. The whole procedure is rapid, entails little bleeding, and is compatible with a duration of ischemia of the cardiac transplant of less than 4 hours.

The histochemical studies performed on the stimulated LDM biopsy specimens showed full transformation of glycolytic fibers into fatigue-resistant oxidative fibers and, therefore, confirmed the electrophysiologic principle of cardiomyoplasty in humans [14].

Our observation shows that cardiomyoplasty is not a therapeutic dead-end, an important fact from the ethical standpoint.

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INVITED COMMENTARY

The report of Dr Jegaden and associates is of critical importance in demonstrating that cardiomyoplasty does not preclude subsequent cardiac transplantation.

Dr Jegaden and associates have mentioned the major adhesions of the muscle to the posterior sternum and adjacent structures, and I readily agree with their findings, having noted similar findings on patients who experienced late death. As a result of this, my colleagues and I are now evaluating covering the muscle with a layer of Teflon, which has been successful experimentally in preventing adhesions in the mediastinum. It is important to note that Jegaden and associates confirmed conversion of the type of fibers, but lack demonstrative patient improvement other than NYHA classification. This has been true of most of the data reported in close to 200 cases throughout the worldwide literature, and I believe it is impeding progress in this field.

Dr Jegaden and associates state that they did not understand the mechanism of cardiomyoplasty, whether it functions in the systolic phase in increasing contractility or in the diastolic in preventing overdistention. I would agree with them to the extent that it is not a circumferential squeezing. The length of the muscle when it is transected is reduced by one-third and, in a large dilated heart, as shown in this case, simply cannot fully encompass the circumference of the right and left ventricle. In addition, our results have indicated that improvement in ejection fraction is due to the compression of the affected wall area, particularly the anterior lateral wall, much as one would do during external compression. I believe that the geometric configuration of the muscle wrap in this case, being placed in the posterior location, was probably less efficacious than it could have been if placed in an anterolateral wrap, where the most viable contractile force of the latissimus muscle would be anteriorly. In this type of geometric configuration, where the anterior lateral wall was the most seriously impaired, we would favor using the right latissimus dorsi, placing this anteriorly over the right and left ventricles and attaching it to the pericardium as far posterior as possible in the area of the atrioventricular groove.

It should also be noted that although heart size is important, physiological data are more helpful in selecting patients. In the 20 clinical cases we have performed, 6 of our 7 long-term survivors (6 months to 5 years) have had a right latissimus anterior wrap and preserved right ventricular function with a preoperative ejection fraction of 0.35 and a left ventricular ejection greater than 0.20. The overall improvement in *left* ventricular ejection fraction in this group has been from an average of 0.27 preoperatively to 0.38 postoperatively.

In summary, I congratulate Dr Jegaden and associates for their recognition of the fact that in this particular case cardiomyoplasty was not effective and for proceeding to successful cardiac transplantation.

This case points out the continuing progression of knowledge we are gaining with cardiomyoplasty and the exciting avenues of research it will provide for the younger cardiac surgeons in the entire field of muscle plasticity.

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Vascular Ring: Does Magnetic Resonance Imaging Replace Angiography?

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The records of 21 patients who underwent operation for symptoms attributable to vascular ring were reviewed. The study covered 33 years, 1958 to 1991, and the mean follow-up was 6.8 years. The patients ranged from 7 days to 26 years old with a mean age of 2.9 years. Twenty patients were symptomatic. Symptoms were due to tracheal compression in 16 patients, esophageal compression in 2, and both causes in 2. During the first 30 years, chest roentgenography, barium swallow, and aortography constituted the diagnostic workup in the majority of the patients. During the last 3 years, magnetic resonance imaging replaced aortography. The surgical diagnosis included five variants of vascular ring. The surgical approach consisted of left thoracotomy in 19 patients and right thoracotomy in 2. These 2 had the diagnosis of right aortic arch with posterior left subclavian artery. In both instances, preoperative angiographic data determined the surgical approach. Barium swallow may be sufficient for the diagnosis of vascular ring; however, additional data are useful in determining the surgical approach. Magnetic resonance imaging can yield accurate data without subjecting the patient to the risks associated with angiography.

(*Ann Thorac Surg* 1992;53:882–5)

The two earliest reports of tracheal or esophageal compression by a vascular structure are credited to Bayford [1] in 1794 and Hommel in 1737 [2]. Bayford described a retroesophageal right subclavian artery and Hommel, a double aortic arch. Surgical correction of this anomaly was suggested by Jex-Blake based on autopsy findings in a puppy that had documented stridor and dysphagia. In 1945, Gross [3] reported the first successful surgical correction of a vascular ring, the division of a double aortic arch. Subsequently a variety of vascular rings have been reported including double arch, right arch with posterior right or left subclavian artery, left arch with anomalous subclavian branches, anomalous ligamentum arteriosum, and anomalous innominate artery [4–7]. The establishment of a diagnosis of vascular ring requires a high index of suspicion [8, 9], and evaluation has included chest roentgenography, barium swallow, and arch angiography when further anatomical detail is needed. In our series, magnetic resonance imaging (MRI) has been used since 1988 to obtain information previously gained with angiography.

The clinical advantages associated with MRI have led us to use this test instead of angiography. To objectively analyze this diagnostic approach, we retrospectively reviewed our experience with vascular rings over the last 33 years.

Material and Methods

The charts of all patients undergoing operation for symptomatic great-vessel anomalies from 1956 through 1991 were reviewed. The following data were obtained: presenting age, presenting symptoms, diagnostic tests performed, associated anomalies, anatomy of the arch determined at operation, postoperative course, and complications. Follow-up of the study population was done. Data were analyzed using χ^2 analysis with 2 × 2 contingency tables where appropriate.

Results

During this period, 21 patients underwent surgical correction of vascular ring anomalies. Twenty patients had a variant of vascular ring, and 1 patient had an anomalous left pulmonary artery. The mean age of the 20 patients with a vascular ring was 2.9 years. The patient with the pulmonary sling was 2 days old. There was an approximately equal number of male and female patients. No patient had an associated cardiac anomaly or esophageal atresia. Two of the children had trisomy 21.

Presenting symptoms were pneumonia, wheezing, stridor, upper respiratory infection, gastroesophageal reflux, dysphagia, and failure to thrive (Table 1). All patients underwent chest roentgenography as part of the initial workup. Ninety-five percent of the group underwent barium swallow, 70% underwent aortic angiography, and 15% had MRI. The only patient not to undergo a barium swallow had MRI. In 15%, a barium swallow was the only test other than chest roentgenography (see Table 1).

All patients were explored through a posterolateral thoracotomy, 19 through a left approach and 2 through a

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Table 1. Categorization of Patients by Date of Presentation Symptoms, Workup, and Diagnosis

Years	No. of Patients[a]	Symptoms	Workup	Diagnosis
1955–1959	2	Pneumonia	Barium	RA with posterior LSA
		Stridor, wheezing	Barium, angiography	Aberrant RSA
1960–1964	3	Upper respiratory infection	Barium	RA with posterior LSA
		Stridor, pneumonia	Barium	Double arch
		Gastroesophageal reflux	Barium, angiography	RA with posterior LSA
1965–1969	4	Stridor, gastroesophageal reflux	Barium	Double arch
		Stridor gastroesophageal reflux	Barium, angiography	Aberrant innominate
		Stridor, upper respiratory infection	Barium, angiography	RA with posterior LSA
		Stridor	Barium, angiography	Double arch
1970–1974	2	Stridor	Barium, angiography	RA with posterior LSA
		Wheezing, stridor	Barium, angiography	Double arch
1975–1979	2	Gastroesophageal reflux, failure to thrive	Barium, angiography	RA with posterior LSA
		Wheezing, upper respiratory infection	Barium, angiography	RA with posterior LSA
1980–1984	1	Wheezing, stridor	Barium, angiography	RA with posterior LSA
1985–1989	6	Pneumonia	Barium, angiography	RA with posterior LSA
		Wheezing	Barium, MRI	RA with posterior LSA
		Wheezing, dysphagia	Angiography, MRI	RA with posterior LSA
		Stridor	MRI	RA with posterior LSA
		Wheezing, stridor	Barium, angiography	RA with posterior LSA
		Wheezing, upper respiratory infection	Barium, angiography	RA with posterior LSA

[a] Patient with posterior left pulmonary artery is not included.

Barium = barium swallow; LSA = left subclavian artery; MRI = magnetic resonance imaging; RA = right arch; RSA = right subclavian artery.

right approach. Anatomy was grouped into one of six categories (see Table 1). Right aortic arch with a posterior left subclavian artery, found in 70% of the patient population, was the most common anatomical variant. Double aortic arch was present in 20%. One patient (5%) had an aberrant right subclavian artery, and 1 had an aberrant innominate artery. All operations were performed electively except for that involving the infant with anomalous left pulmonary artery who underwent operation on an urgent basis for respiratory insufficiency.

Six patients were evaluated without the use of angiography. The remaining 14 underwent aortic angiography with or without cardiac catheterization. The mean length of hospitalization for those who underwent an invasive vascular workup was 9.53 days compared with 5.83 days for those who had an entirely noninvasive evaluation ($p < 0.05$).

Surgical correction of the vascular ring consisted of extensive mobilization, division, and ligation of the ligamentum arteriosum for patients with right arch and posterior left subclavian artery. Division of the atrophic arch adequately treated double aortic arch. The anomalous innominate artery was suspended to the posterior aspect of the sternum, as described by Gross and Neuhaurer [6]. The one aberrant right subclavian artery had its origin directly from the aorta anteriorly between the takeoff of the left carotid and left subclavian arteries. This vessel coursed anterior to the trachea and then traveled posteriorly and to the right to take its normal position. By suspending this vessel from the posterior aspect of the sternum, tracheal compression was relieved.

There was 1 postoperative death and 1 postoperative complication (respiratory insufficiency requiring emergency tracheostomy). Both were attributable to aspiration in the immediate postoperative period. The 20 survivors were followed up long term. Follow-up ranged from 6 months to 18 years (mean follow-up, 6.8 years). All children had complete resolution of symptoms. All had normal growth curves. There were no instances of symptomatic tracheomalacia.

Comment

The diagnosis of vascular ring can be entertained only when there is a strong clinical suspicion. When a child is being evaluated for reflux or wheezing, a vascular ring should be included in the differential diagnosis, particularly when the chest roentgenogram shows abnormal

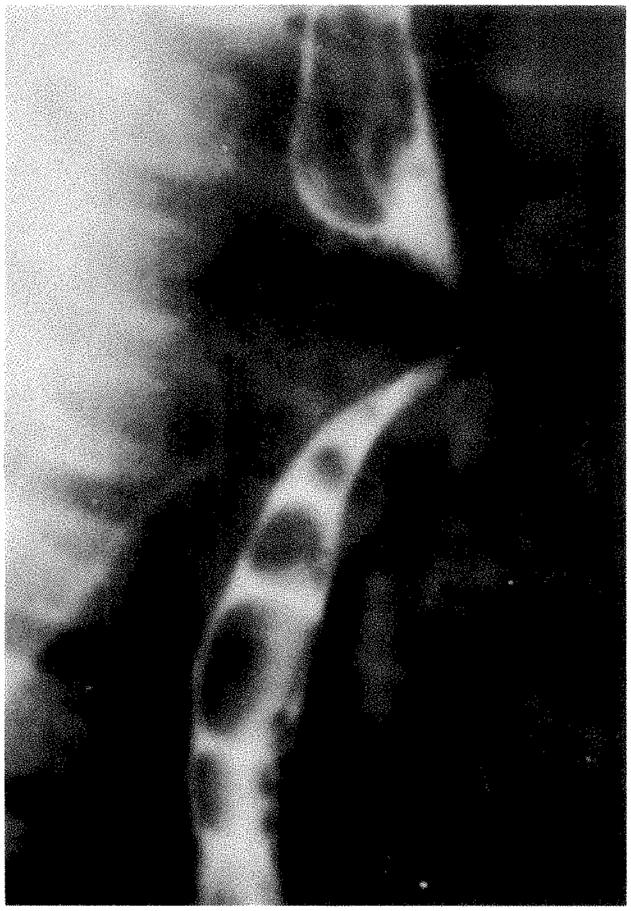

Fig 1. Barium swallow of a child with double aortic arch.

narrowing of the trachea, an abnormality in the mediastinum, or obliteration of the esophageal stripe [10]. These findings can be subtle on a plain chest roentgenogram. Thus, the evaluating physician often must rule out vascular ring in the face of a normal-appearing chest roentgenogram.

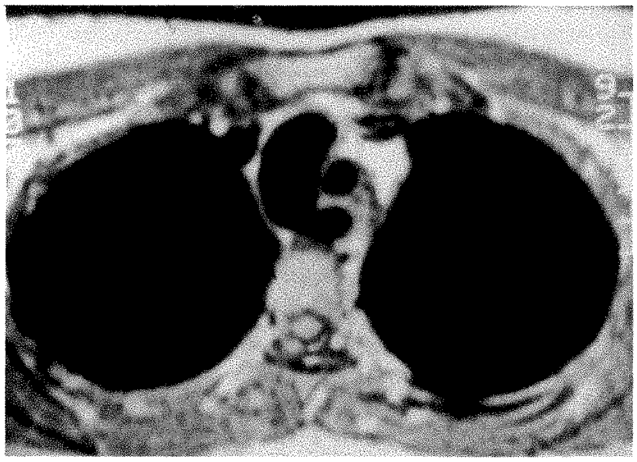

Fig 2. Transverse magnetic resonance image of a teenager with a right aortic arch and a posterior left subclavian artery. Note that the left subclavian artery is seen in its usual location at the thoracic outlet. A posterior right subclavian artery may not be visualized in a single scan.

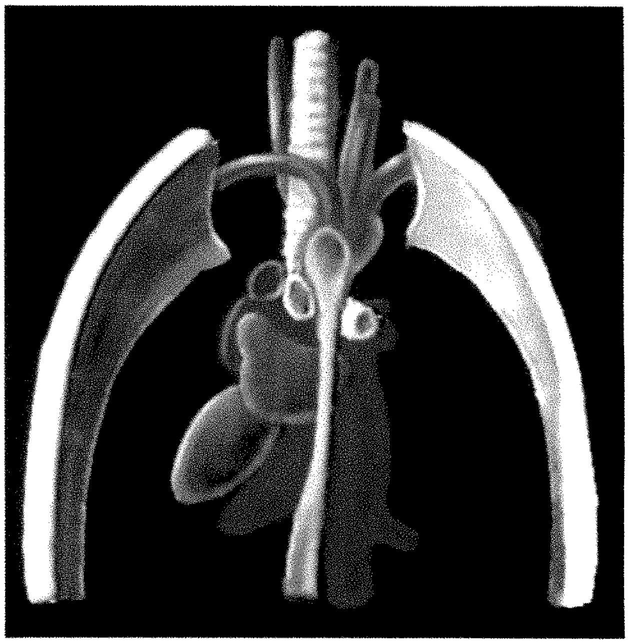

Fig 3. Three-dimensional reconstruction of the magnetic resonance images associated with Figure 2 (posterior view). The origin of the left subclavian artery is posterior to the trachea. Note that the esophagus is filtered out at the level of the aortic arch.

The workup of vascular ring has traditionally included a barium swallow, an aortic angiogram, or both. Several authors [11–15] have suggested that a barium swallow is sufficient to establish the diagnosis (Fig 1). However, certain forms of vascular ring cannot be clearly defined by barium swallow [11, 12]. Although the majority of these

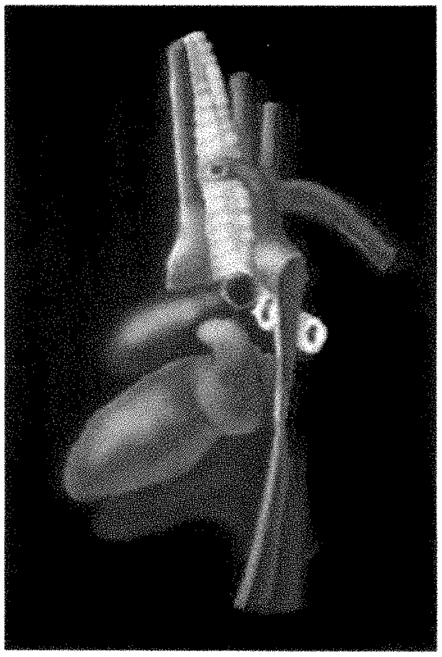

Fig 4. Lateral projection of the image in Figure 3. The vascular ring in this patient was completed by the ligamentum arteriosum extending from the left subclavian origin to the pulmonary artery.

anomalies can be approached and treated through a left thoracotomy, anomalies such as left aortic arch with a right ligamentum arteriosum should be approached through a right thoracotomy. If such anomalies cannot be excluded by barium swallow, further study is indicated.

Angiography defines the vascular structures, enabling the surgeon to select the appropriate surgical approach. However, this invasive procedure has several drawbacks. First, angiography is associated with allergic reactions, embolic phenomena, and vascular injury at the arterial puncture site [10]. Second, in the pediatric population, angiography necessitates hospital admission and can necessitate general anesthesia for its performance. Third, the recovery after angiography is labor intensive and includes immobilization and frequent evaluation for vascular insufficiency. Finally, a radiation dose is administered with angiography but not with MRI. We found that when angiography was performed during the same hospitalization as operation, patients not undergoing angiography had a significantly shorter hospitalization ($p < 0.05$).

Magnetic resonance imaging provides all the anatomical detail needed to treat vascular rings. It will supply anatomical detail of structures not seen with angiography, such as the ligamentum arteriosum. During the past 3 years, MRI at our institution has enabled the surgeon to preoperatively evaluate the exact vascular anatomy of the mediastinum without angiography. The anatomy of each ring was evaluated intraoperatively, and our preoperative diagnosis was confirmed in each instance. In addition, the pulmonary vasculature was clearly visualized in each patient undergoing MRI. This is important, as both hypoplastic and absent pulmonary arteries have been described in patients with vascular rings [11, 12]. Such preoperative information is important when performing these operative procedures and cannot be gleaned from aortography without right heart catheterization.

Considering the diversity in vascular ring anomalies, there are instances when preoperative knowledge of the surgical anatomy is extremely useful. As already discussed, MRI is particularly suited to this task (Fig 2) [16–18]. It is especially helpful to use standard computer software packages to convert a series of two-dimensional MRI images into a three-dimensional anatomical model. Such models can be rotated about any axis to reveal anatomical subtleties that might otherwise be difficult to visualize [19]. Figures 3 and 4 are examples of three-dimensional computerized images created with serial MRI scans. These three-dimensional images can help a surgeon visualize preoperatively the anatomy that is to be addressed. We think that although it is still expensive and not widely available, three-dimensional imaging represents the future of diagnostic imaging of the great vessels. As computer technology progresses, the software necessary for this kind of reconstruction will most probably become an integral part of computerized imaging. We recognize that three-dimensional modeling is not essential, but it does illustrate complex anatomy in an exceptionally clear and straightforward manner.

We conclude that MRI should be the diagnostic test of choice for vascular rings. It provides the information available from angiography as well as details of the pulmonary circulation and nonvascular structures. The use of MRI in place of angiography shortens the hospital stay, decreases morbidity, and accurately describes the anatomy necessary for precise surgical correction.

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Aortic Dissection Without Intimal Rupture: Diagnosis and Management

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A 59-year-old man had symptoms of aortic dissection. Computed tomography and angiography showed a large intramural hematoma of the ascending and descending aorta without intimal defect or false lumen. The hematoma resolved completely within 7 weeks with medical treatment. His symptoms recurred 6 months later. Computed tomography and angiography demonstrated a type B dissection with a false lumen and an intimal defect. This case illustrated the progressive nature of aortic dissection without intimal rupture. The diagnostic criteria and therapeutic options are discussed.

(*Ann Thorac Surg 1992;53:886–8*)

A 59-year-old man had acute onset of sharp tearing interscapular pain after heavy lifting. A similar episode happened 3 years previously requiring hospitalization for 5 days; however, no definitive diagnosis was made. On examination his blood pressure was 220/115 mm Hg from both arms and his pulse was 78 beats/min and regular. There was no pulse deficit or cardiac murmur, and there was no neurologic deficit. Laboratory investigations including complete blood count and measurement of electrolytes, blood urea nitrogen, creatinine, creatine kinase, and leukocyte dehydrogenase were normal. A 12-lead electrocardiogram showed normal sinus rhythm with no ischemic changes nor previous myocardial necrosis. Chest roentgenogram showed, however, a prominent superior mediastinum, a left perisubclavian hematoma, and no pleural effusion. There was no family history of coronary artery disease or Marfan's syndrome. His significant past medical history included poorly controlled hypertension for approximately 3 years and a 30 pack-year history of cigarette smoking. There was no history of sexually transmitted disease.

Initial investigations for aortic dissection included transthoracic two-dimensional echocardiography, which showed a dilated aortic root (6 cm external diameter) with a tricuspid aortic valve and no aortic insufficiency. Both ventricles contracted well and there was no evidence of pericardial effusion. An aortic arch angiogram showed an abnormal contour of the proximal descending thoracic aorta (DTA) with marked circumferential widening and flattening of the lumen, suggesting extensive intramural hematoma. The ascending and transverse aorta were also ectatic with moderate mural thickening. There was no evidence of intimal flap, false channel, or penetrating atheromatous ulcer (PAU) (Fig 1). Computed tomography (CT) with intravenous contrast medium and a 1.5-cm slice thickness confirmed the nonenhancing crescentic intramural hematoma involving the ascending, transverse, and descending thoracic aorta. Again no intimal tear, false channel, or PAU was identified (Fig 2).

Due to the extensive involvement of the aorta and absence of intimal tear or false channel, we elected to manage him medically. Initially he was given intravenous nitroprusside and labetalol, and subsequently oral metoprolol and nifedipine were given with complete resolution of symptoms. Digital subtraction aortogram and CT on hospital day 10 demonstrated partial resolution of the intramural hematoma. He was discharged 16 days after admission.

Repeat CT with intravenous contrast medium 5 weeks later in clinic showed almost complete resolution of the extensive aortic intramural hematoma with minimal thickening of the aortic wall (Fig 3). However, 6 months after his initial presentation, he experienced back pain again after some heavy lifting. A digital subtraction aortogram and CT with intravenous contrast medium demonstrated a type B aortic dissection extending from the proximal DTA to the abdominal aorta above the celiac axis. A small left pleural effusion was seen (Fig 4). The ascending and transverse aorta were not involved, and there was no aortic insufficiency. At operation the proximal DTA was replaced by a 10-cm-long Dacron graft through a left posterolateral thoracotomy. Intraoperative inspection of the DTA confirmed the extensive subadventitial hematoma (external diameter, 8 cm). The intima was atherosclerotic, and a discrete 1 × 1.5-cm defect was identified posterolaterally and 15 cm distal to the left subclavian artery. He recovered well without neurologic complications and was discharged on postoperative day 12. An aortic digital subtraction aortogram obtained before discharge demonstrated no residual false channel. Follow-up at 1 month showed good recovery. Periodic follow-up with CT surveillance in the future is planned.

Comment

Dissections of the aorta are conventionally classified into either type I, II, or III as described by DeBakey and associates or type A and B as described by Daley and colleagues. The etiology of aortic dissection was believed to be degeneration of the aortic media (cystic medial necrosis) associated with Marfan's disease or other inherited connective tissue disorders. However, Larson and Edwards [1] showed that only a few patients among 161

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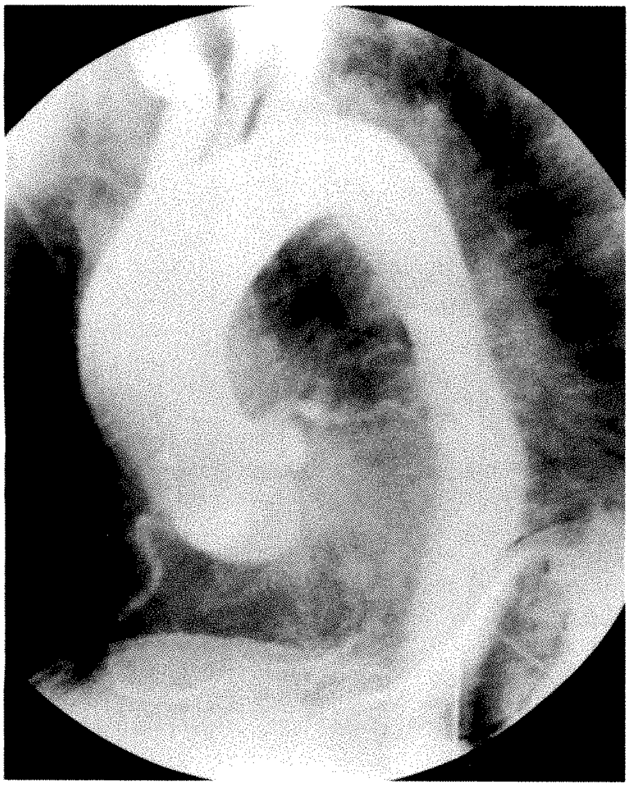


Fig 1. Thoracic aortogram showing an abnormal contour of the proximal descending aorta with marked circumferential widening and narrowing of the lumen, suggesting extensive intramural hematoma (June 2, 1990).

autopsies of patients with known aortic dissection had these classic changes. The same authors also found intimal tears in each of the 158 autopsies they examined, thus providing support to the concept of the primacy of the intimal tear proposed by Murray and Edwards [2]. A number of predisposing factors associated with aortic dissection have been identified, including hypertension, pregnancy, bicuspid aortic valve, aortic coarctation, blunt chest trauma, and cardiac surgical procedures.

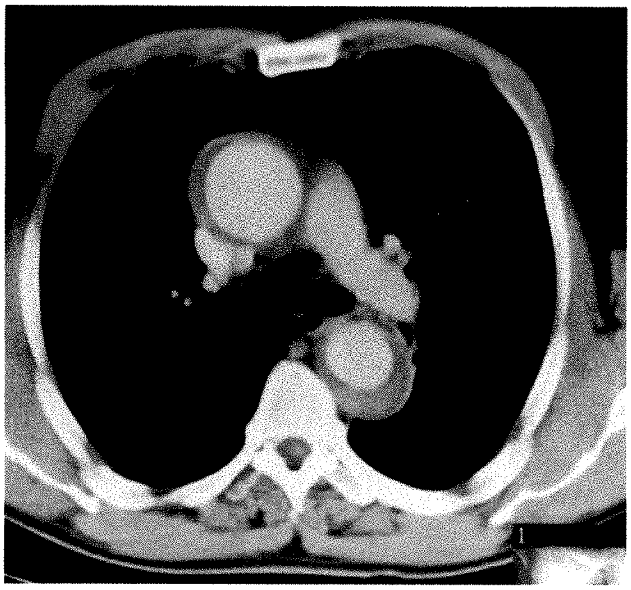


Fig 2. Representative computed tomogram of the thorax with intravenous contrast medium showing aortic intramural hematoma. No intimal defect, false channel, or penetrating atheromatous ulcer could be identified (June 2, 1990).

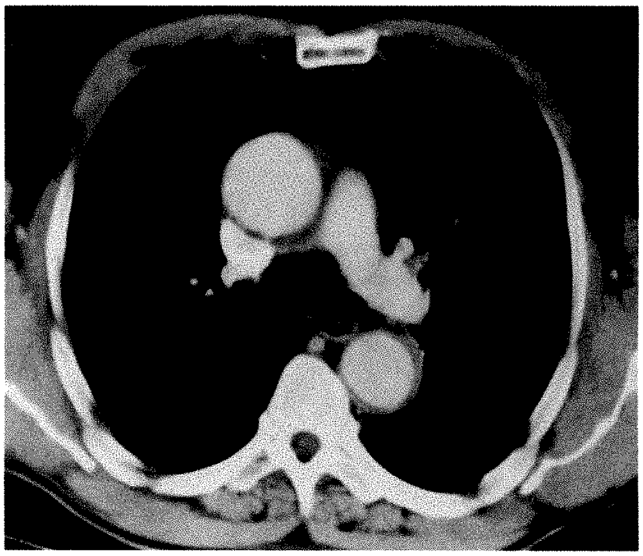
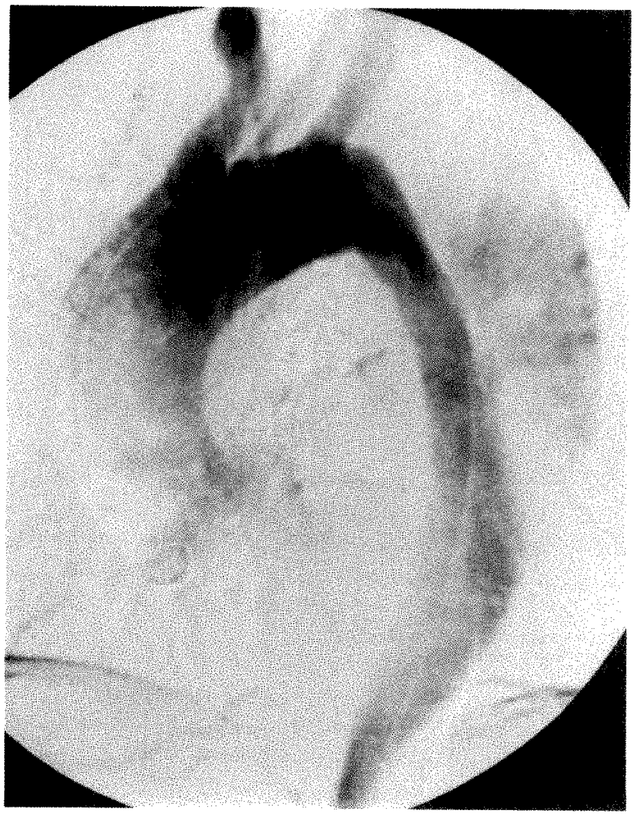


Fig 3. Representative computed tomogram of the thorax with intravenous contrast medium showing almost complete resolution of the aortic intramural hematoma with minimal residual thickening of the aortic wall (July 22, 1990).

During the last decade, two atypical mechanisms of aortic dissection with distinct radiographic appearance have been reported. In 1984, Stanson and associates [3] proposed a new mechanism of aortic dissection of the DTA due to "penetrating atheromatous ulcer." This pathologic entity of the aorta was subsequently confirmed by authors from several other institutions [4, 5]. It is characterized histopathologically by extensive atherosclerosis of the DTA with an atheromatous ulcer (or ulcers) penetrating the internal elastic lamina and hematoma formation within the media of the aortic wall. Several specific CT scan and angiographic features have been identified to differentiate aortic dissection due to PAU from classic aortic dissection: (1) presence of the ulcer or ulcers and intramural hematoma and (2) absence of intimal flap and dissecting false channel. Contrary to classic type B aortic dissection, where the intimal defect is almost always located immediately distal to the left subclavian artery, aortic dissection due to PAU almost always occurs at the middle or lower DTA. In Stanson and associates' [3] series of 16 patients with aortic dissection due to PAU, 14 patients underwent operation with an operative mortality of 7.2%, and postoperative paraplegia developed in 4 patients (28%). Short-term success with medical treatment of 5 patients with dissection of the DTA from PAU has also been reported [5].

In 1985, Yamada and associates [6, 7] proposed a new variety of aortic dissection, which they called "aortic dissection without intimal rupture" (AD-IR). The etiology of AD-IR was believed to be due to rupture of the vasa vasorum of the aortic wall resulting in hematoma dissect-



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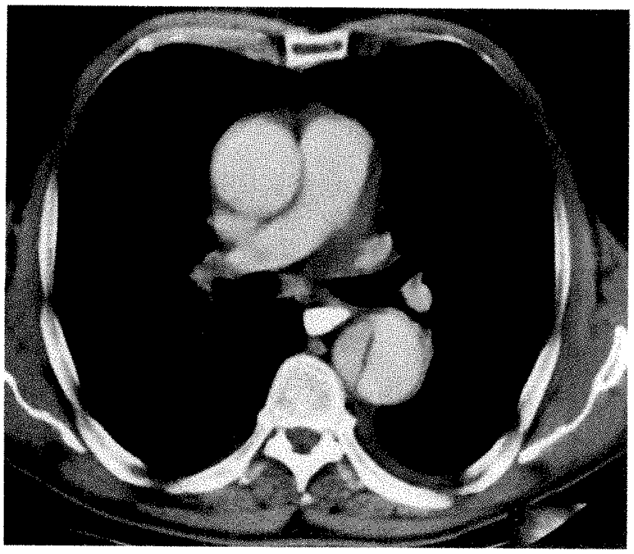

B

Fig 4. (A) Digital subtraction angiogram of the thoracic aorta showing type B aortic dissection with true and false lumen (Nov 1990). (B) Representative computed tomogram of the thorax with intravenous contrast medium showing type B aortic dissection with false lumen beginning distal to the left subclavian artery and left pleural effusion (Nov 1990).

ing along the plane between the outer media and adventitia, a theory proposed by Wilson and Hutchins [8] in 1982. Characteristically, plain CT in patients with AD-IR shows continuous, crescentic high-attenuation areas along the wall of the aorta without evidence of intimal defect or dissecting false lumen. In the CT with contrast medium, the same crescentic area (intramural hematoma) fails to enhance, indicating that it does not communicate with the aortic lumen. It is differentiated from aortic dissection due to PAU by the lack of demonstrable ulceration of the aortic wall as well as the intactness of the intima. Six of the 14 patients in the series reported by Yamada and associates [6] had type A dissection (43%), and the remaining 8 patients had type B dissection. All of the patients were managed medically and followed up periodically with CT or magnetic resonance imaging. Three patients (21%) died within 1 month of diagnosis (2 type A, 1 type B). A fourth patient (type B) died during follow-up of an attempted graft replacement of the DTA when his aortic intramural hematoma expanded rapidly. Nine of the 10 survivors showed complete resolution of the aortic intramural hematoma with normal appearance of the aortic wall by CT within 1 year. The combined mortality rate for this series with a nonoperative approach was 28.6% (33.3% for type A dissection). Autopsy findings in 2 patients (both type A dissection) confirmed the atherosclerotic but intact intima and hematoma formation between the outer media and the adventitia.

None of the four CT studies in our patient identified any PAU. Granted, a small PAU less than 1.5 cm could be easily missed between slices; however, multiple views of the initial aortogram and the two subsequent aortic DSA also failed to show a PAU, supporting AD-IR as the underlying pathology of our patient's aortic dissection. Our patient's protracted clinical course, commencing 3 years ago, and its final progression to a conventional aortic dissection raise the interesting question of whether AD-IR truly represents a different pathology or simply the precursor of the conventional aortic dissection. More clinical observations in the future will hopefully elucidate the true natural history of this aortic disease and thus provide some guidelines regarding the proper management.

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Megaaorta and Aortoiliac Obstruction: Alternate Method of Cannulation

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The case of a 69-year-old man with aneurysms of the ascending aorta, transverse aortic arch, and thoracoabdominal aorta combined with coronary artery disease, aortic insufficiency, and severe aortoiliac occlusive disease is presented. Femoral arterial cannulation was contraindicated owing to the aortoiliac disease. Successful surgical treatment is described using an alternate method of cannulation and perfusion.

(Ann Thorac Surg 1992;53:889–91)

Aneurysms of the ascending aorta, aortic arch, and thoracoabdominal aorta are routinely repaired by a staged procedure. This includes repair of the ascending aorta and aortic arch in the first procedure, followed by repair of the thoracoabdominal aorta. The first stage of the operation is carried out under cardiopulmonary bypass with perfusion from one of the femoral arteries. In patients with atherosclerotic occlusive disease of the distal aorta and iliac arteries who require ascending aorta or

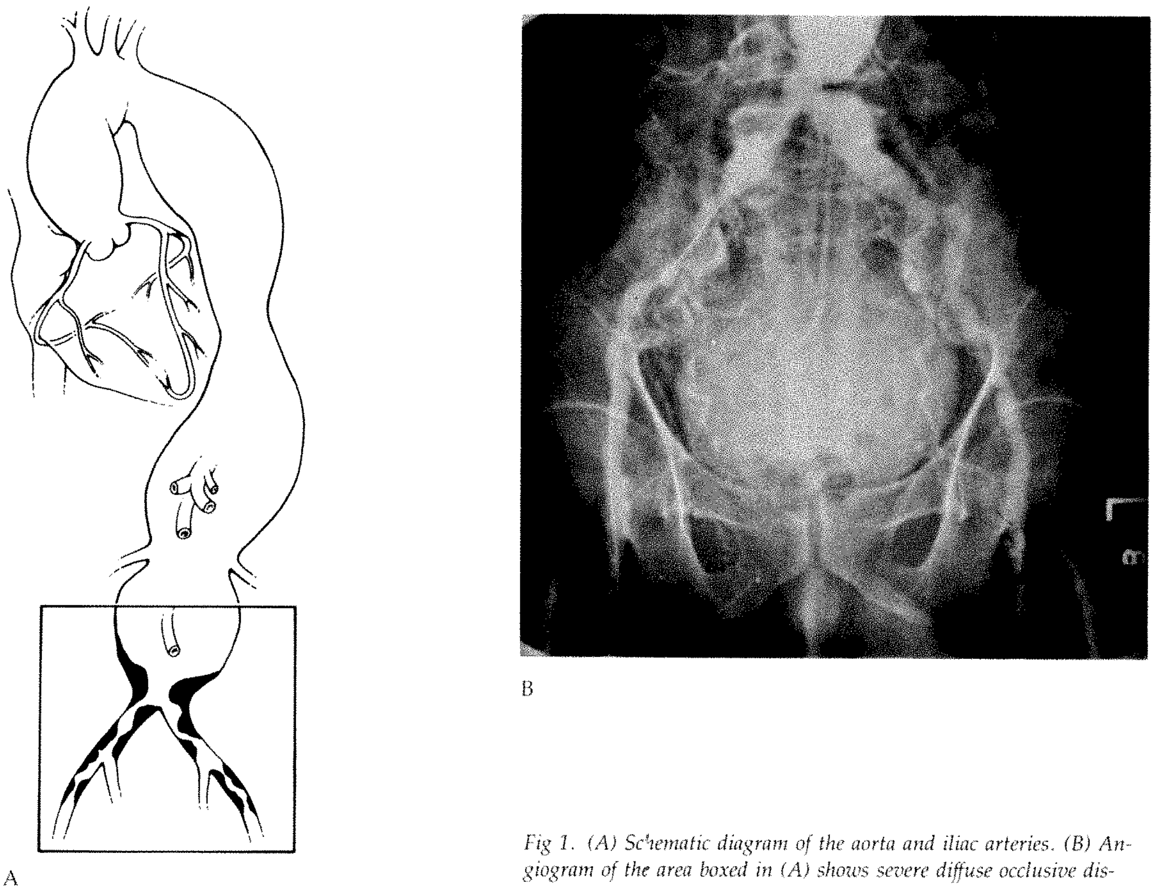

Fig 1. (A) Schematic diagram of the aorta and iliac arteries. (B) Angiogram of the area boxed in (A) shows severe diffuse occlusive disease.

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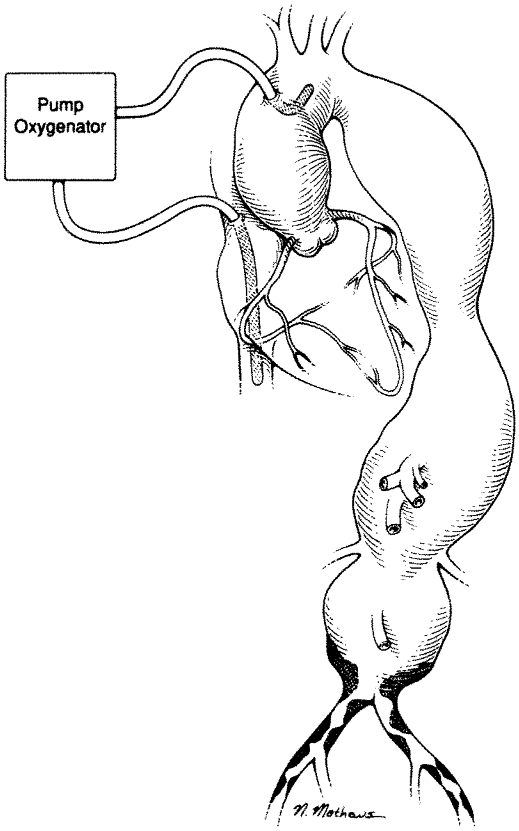

Fig 2. Aortic cannulation through the ascending aortic aneurysm.

aortic arch replacement, alternate methods of cannulation and perfusion have been described. Coselli and Crawford [1] have reported resection and graft replacement of the abdominal aorta and perfusion through a femoral graft. There are patients, however, in whom this option is less than optimal. We describe a patient in whom a megaaorta was encountered combined with severe distal aortoiliac occlusive disease in whom an alternate method of cannulation and perfusion was necessary because of the unusual combination of disease processes and the problems that they posed.

A 69-year-old, nondiabetic, chronically hypertensive male smoker was found by chest roentgenogram and computed tomographic scan to have aneurysms of the ascending aorta, aortic arch, and thoracoabdominal aorta. His only complaints were of occasional chest pains and an increasing cough. He also admitted to one-half block claudication bilaterally. He was referred for surgical evaluation. Studies, including computed tomographic scans of the chest and abdomen, aortography, cardiac catheterization, transthoracic echocardiography, and pulmonary function tests, revealed the patient to have a multitude of pathology (Fig 1) including transverse arch and ascending aortic aneurysms, an extensive thoracoabdominal aortic aneurysm (Crawford type II), moderate aortic insufficiency, severe single-vessel coronary artery disease, severe aortoiliac occlusive disease, and chronic obstructive pulmonary disease with chronic bronchitis.

The patient was subsequently explored through a median sternotomy. Transesophageal echocardiography and epicardial echocardiography at the time of operation revealed the patient to have 2+ aortic insufficiency and moderate aortic sclerosis, a 6.5-cm ascending/arch aneurysm, and a 7.0-cm descending thoracic aneurysm. Thrombus was noted in the descending thoracic aorta; however, the ascending aorta was noted to be free of calcium and thrombus. The sinus portion of the ascending aorta was not aneurysmal. The patient was heparinized, and routine cannulation was undertaken using single aortic and atrial cannulas. The aortic cannula was placed in the ascending aorta at the base of the innominate artery (Fig 2).

The patient was placed on cardiopulmonary bypass and cooling was begun. The left ventricle was vented through the right superior pulmonary vein. The circumflex coronary artery, which had been noted preoperatively to have an 80% stenosis, was bypassed during ventricular fibrillation with reversed autogenous saphenous vein. During this period distention developed in the heart secondary to aortic insufficiency despite 1,500 mL/min of return from a left ventricular vent. Therefore, the aorta was cross-clamped and opened. Myocardial protection was achieved with antegrade cold blood cardioplegia given directly into the coronary ostia followed by intermittent cold blood cardioplegia through the coronary sinus. The aortic valve was inspected and noted to be sclerotic with poor central coaptation. The valve was resected and replaced with a 25-mm Carpentier-Edwards porcine valve.

When the rectal temperature reached 17°C, the electroencephalogram showed no activity. The patient was

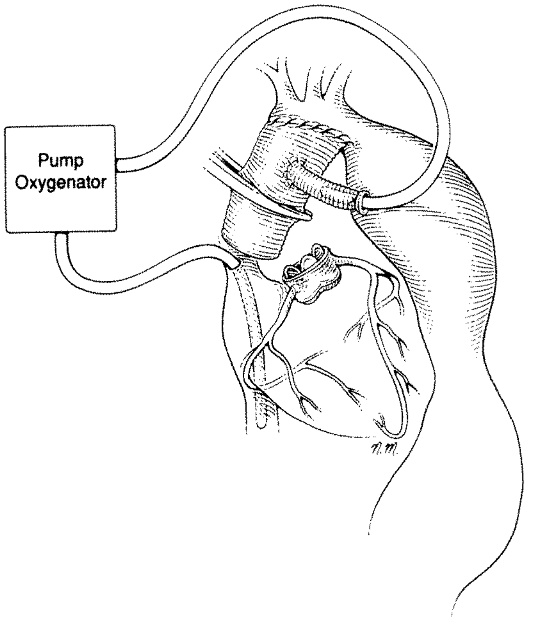

Fig 3. The method of cannulation and perfusion after circulatory arrest and arch replacement. A 25-mm porcine aortic valve has been inserted and a 12-mm Dacron graft has been sewn to the ascending graft. Aortic flow is reestablished by securing the aortic cannula within the 12-mm graft.

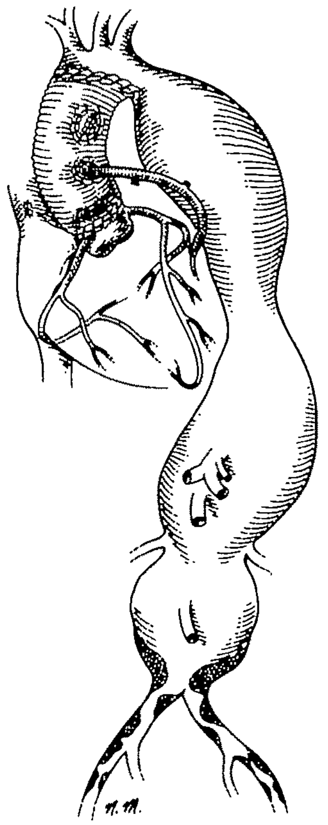

Fig 4. Schematic diagram of the completed operation. The obtuse marginal coronary artery has been bypassed and the vein graft sewn to the ascending graft, and the 12-mm graft has been oversewn at its base.

placed in the head-down position and cardiopulmonary bypass was discontinued. The aortic cross-clamp and ascending aortic cannula were removed and, without clamping of the arch vessels, the ascending aortic aneurysm along with the majority of the arch of the aorta were resected. These were replaced with a 30-mm woven Dacron tube graft that had been previously baked in albumin. After completion of the distal anastomosis, a 12-mm Dacron tube graft was sewn onto the side of the 30-mm Dacron graft. A straight aortic cannula was placed into the 12-mm graft and secured with heavy ties (Fig 3). The pump was gradually turned on, with great care being taken to evacuate all air from both grafts. The distal portion of the ascending graft was clamped, cardiopulmonary bypass was reestablished, and rewarming begun. Total circulatory arrest time was 19 minutes. The proximal aortic anastomosis was then performed in the supracoronary position. Just before completion of this anastomosis, the ascending aorta and aortic graft were deaired and the cross-clamp was removed. The circumflex bypass graft was then sewn end-to-side to the ascending aortic graft using partial occlusion. After rewarming, the patient returned to a normal sinus rhythm and was weaned from cardiopulmonary bypass without problems. The 12-mm Dacron tube graft was clamped at its base, transected, and oversewn (Fig 4).

The patient's postoperative course was without complication and he was discharged home on the seventh postoperative day. After satisfactory recuperation, he returned and had successful replacement of the remainder of his aorta.

Comment

Cannulation of the femoral arteries for perfusion during operations on the ascending and arch of the aorta is almost always possible and preferred. There is the rare patient, however, in whom severe distal aortoiliac occlusive disease prohibits femoral cannulation. Coselli and Crawford [1] have recommended aortoiliac or aortobifemoral bypass grafts with perfusion through one limb of the graft as an alternate technique. The patient presented here, however, had not only aortoiliac occlusive disease but also a large thoracoabdominal aortic aneurysm, which prohibited placement of a simple infrarenal aortic bifurcation graft.

It has been our experience that the vast majority of ascending aortic aneurysms are not lined by thrombus. With advances in transesophageal and intraoperative epicardial echocardiography, clear definition of the ascending aorta and its intraluminal contents is possible and makes cannulation of the ascending aorta in these circumstances relatively safe. The method of placing a separate graft onto the ascending aorta or ascending aortic graft for transthoracic insertion of an intraaortic balloon pump or even perfusion after repair of acute dissections is not new. The adaptation of this technique in this specialized circumstance avoids laparotomy for aortic replacement and the possible complications of poor flow, dissection, and embolization when attempting to perfuse through a severely diseased distal aorta and iliac artery.

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Primary Pulmonary Cryptococcosis Presenting as a Superior Sulcus Tumor

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A patient underwent resection of a superior sulcus tumor after an extensive workup was nondiagnostic. Postoperatively, primary pulmonary cryptococcosis was diagnosed. Management of this patient is presented along with a review of the literature.

(Ann Thorac Surg 1992;53:892–3)

Superior sulcus tumors have become established most commonly to be caused by stage III bronchogenic carcinoma [1]. However, various other neoplastic processes located at the thoracic apex may produce the same clinical and radiological pattern peculiar to superior sulcus tumor. We report a case of primary pulmonary cryptococcosis (PPC) that presented as a superior sulcus tumor.

A 49-year-old man had a 2-month history of pain over the right scapula and posteromedial aspect of the right arm radiating to the ring finger. Neurologic examination revealed decreased sensation to light touch in the T-1 dermatome. Computed tomographic scans of the brain and cervical spine were normal. Chest roentgenogram showed a mass in the apex of the right lung (Fig 1). Computed tomographic scan of the chest confirmed a 4-cm peripheral, apical mass with involvement of the chest wall. A 2-cm right paratracheal lymph node was also noted. Bronchoscopy, tuberculin and coccidioidal skin tests, and cryptococcal serology were normal. Computed tomography–guided needle biopsy of the mass revealed only inflammatory cells.

The patient underwent mediastinoscopy. The results of biopsy of paratracheal and subcarinal lymph nodes were consistent with inflammation. No granulomas were seen. Acid-fast and fungal stains were negative. Because malignancy could not be excluded, the patient underwent resection of the apical mass. This required a right upper lobectomy with en bloc resection of the first three ribs. A fibrotic dense tumor was located at the apex of the right upper lobe, was inseparable from the chest wall, and appeared to be invading the posterior portions of the first and second ribs. Microscopic examination revealed budding yeast forms consistent with cryptococcosis scattered throughout the fibrotic tumor (Fig 2). Postoperatively, evidence of dissemination developed with fever, pulmonary infiltrates, and respiratory insufficiency. The patient responded rapidly to intravenous amphotericin B therapy, receiving a total dose of 1 g. The patient has returned to work and has been asymptomatic for more than 12 months.

Comment

After histoplasmosis, cryptococcosis is the most common cause of death due to mycotic infections [2]. Cryptococcal infection limited to the lungs is defined as PCC. Primary pulmonary cryptococcosis is difficult to diagnose because symptoms and radiological findings are nonspecific, 90% of cases occur in nonimmunosuppressed patients [3], and skin tests are not accurate. Serologic tests have an accuracy of 87% in patients with disseminated cryptococcosis [4], but only 30% in patients with pulmonary masses secondary to PCC [5]. Active PCC is considered to be present if the sputum Gram stain or culture is positive for cryptococcosis and if cavitary, bilateral, or multiple lesions are noted radiographically [6].

Once PCC is diagnosed, postoperative treatment with antifungal agents may be indicated. Three groups of patients should receive postoperative amphotericin B treatment: those with central nervous system involvement, patients with active pulmonary disease, and those who are immunosuppressed [3, 5, 6]. Patients not immunosuppressed with inactive solitary lesions have a 10% risk of development of postoperative cryptococcal meningitis [3]. Most researchers believe these patients can be followed up safely with serial lumbar punctures [5, 6]. Cases of PCC diagnosed nonoperatively are best treated with antifungal agents followed by resection of residual disease in good-risk patients [5]. Cryptococcal meningitis not responsive to amphotericin B can be improved or cured by resection of the pulmonary focus [7] with or without the addition of fluorocytosine [8]. Fluconazole has become used increasingly to treat patients with PCC and to prevent cryptococcal meningitis postoperatively, but fluconazole's efficacy compared with amphotericin has yet to be established [9].

This patient is presented to show that PCC can present clinically and radiologically as a superior sulcus tumor. Resection of the pulmonary mass is often the only way to establish the diagnosis and may not be sufficient to cure PCC without antifungal therapy.

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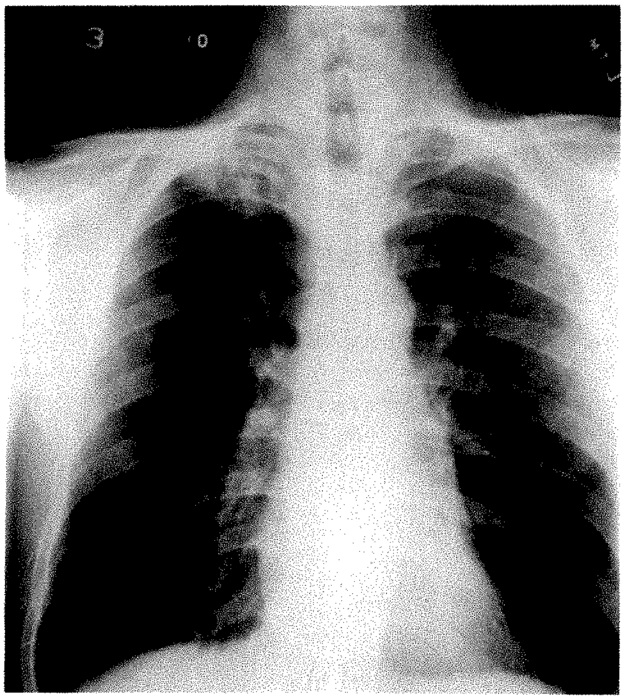

Fig 1. Preoperative chest roentgenogram (posteroanterior view) showing right apical density.

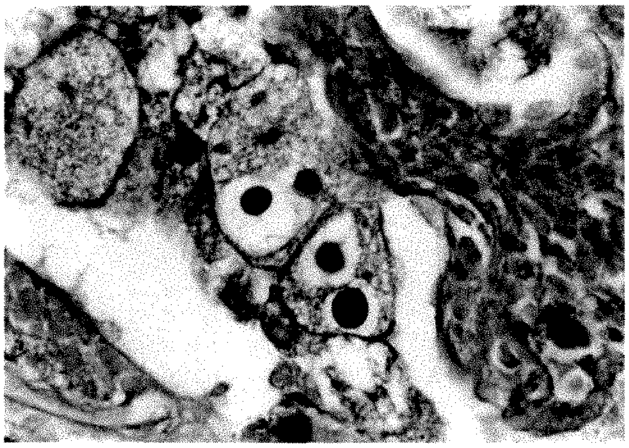

Fig 2. Microscopic section of lung showing organisms within histiocytes. (Periodic acid-Schiff stain; ×400 before 50% reduction.)

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Revascularization for Coronary Ostial Stenosis in Takayasu's Disease With Calcified Aorta

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A case in which a patient with stenoses of the right and left coronary ostia and heavy calcification of the aorta caused by Takayasu's disease was successfully treated by coronary artery bypass grafting is presented. The aortic ends of the two grafts were attached to a xenopericardial patch, which was sutured into the ascending aorta. This technique can be done without fine sutures, which are required for proximal anastomosis of a vein graft, and may reduce the risk of ostial stenosis.

(Ann Thorac Surg 1992;53:894–5)

Takayasu's disease, also known as pulseless disease, affects the aorta and its major branches. Coronary arteries affected by it may require coronary artery bypass grafting. However, calcification of an aorta affected by Takayasu's disease often makes proximal anastomosis of a vein graft very difficult or even impossible. In addition, occlusive or stenotic lesions of the aortic branch vessels prevent the use of arterial grafts for coronary bypass. We report a patient with stenoses of both coronary arterial ostia and heavy aortic calcification caused by Takayasu's disease whose severe angina was relieved by coronary artery bypass grafting using vein grafts. Their proximal ends were sutured into a xenopericardial patch of the ascending aorta.

A 47-year-old woman was referred to the Nagoya University Hospital with severe chest pain, which forced her to have strict bed rest. The patient was diagnosed as having Takayasu's disease at the age of 20 years and had episodes of impaired vision and unconsciousness. Although these symptoms improved, severe chest pains had developed. Upon examination, there was no cardiac murmur audible. The right carotid and both radial pulses were not palpable, and the left carotid and lower limb pulses were normal, although there was a left carotid bruit. The chest roentogenogram showed calcification of the aorta. The electrocardiogram showed inverted T waves in leads V_4 through V_6 with no abnormality in the QRS wave. The digital subtraction angiogram of the aortic arch and its branch vessels showed stenoses of the left carotid and right subclavian arteries. The right carotid and left subclavian arteries were occluded. The coronary angiogram revealed stenoses of both the coronary ostia (Figs 1A, B). Computed tomography of the chest showed heavy calcification of the thoracic aorta (Fig 2). Because of coronary angiographic evidence of bilateral ostial stenoses and severe chest pain, coronary bypass grafting to the right and left coronary arteries was necessary.

During the operation, the wall of the ascending aorta and aortic arch was detected to be as hard as stone. An arterial cannula was inserted into the right femoral artery and cardiopulmonary bypass was started. A suitable site for proximal anastomosis of vein grafts could not be found. To avoid fine sutures at the proximal anastomosis, two vein grafts were first attached to an oval piece of glutaraldehyde-preserved xenopericardial patch (Fig 3). The two grafts then were anastomosed to the right and left coronary arteries, respectively. The aorta was slit up at its root using heavy scissors and small rongeurs. The method of preparation of the ascending aorta for proximal graft insertion in this patient was to crack the calcified aortic intima along the suture line, being careful not to tear off the adventitia, and to remove a small amount of calcified intima at the cut edge of the aorta. The sutures were passed through the cracks. The patch was sewn into the slit of the aortic root with 4-0 Prolene (Ethicon, Somerville, NJ) running sutures.

No complications developed postoperatively. The coronary arteriogram showed functioning vein grafts 2 months after operation (Figs 1C, D). The patient has had no recurrence of angina pectoris during the 15 months since the operation.

Comment

Takayasu's disease is a disease of unknown etiology that affects the aorta and its branch vessels. Histological changes are initially granulomatous inflammation, which is caused by the inflammation of the vasa vasorum, and later intimal thickening or heavy calcification. These disorders cause aortic regurgitation, coronary artery lesions, and dilatation or stenosis of the aorta, some of which require surgical treatment [1]. In patients with angina pectoris, coronary artery bypass grafting is required. However, the selection of graft material for a patient with Takayasu's disease is controversial. As the branch vessels of the aorta are often affected by Takayasu's disease, vein

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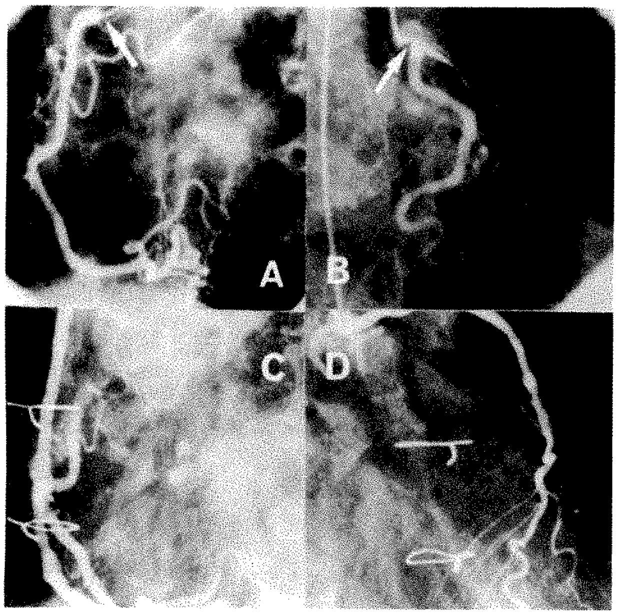

Fig 1. Preoperative right (A) and left (B) coronary angiograms show ostial stenoses (arrows) *of both coronary arteries. Postoperative coronary angiograms show functioning vein grafts to the right (C) and left (D) coronary arteries.*

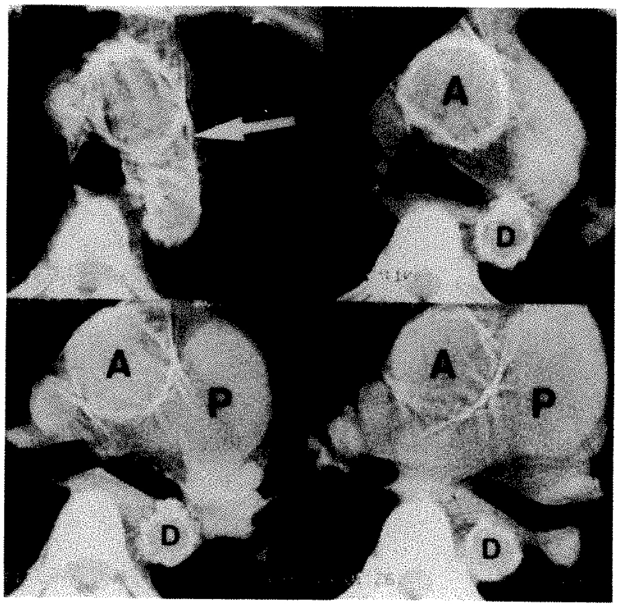

Fig 2. Computed tomogram of the thoracic aorta shows circumferential heavy calcification of the aortic wall. An arrow *shows the aortic arch.* (A = *ascending aorta;* D = *descending aorta;* P = *pulmonary artery.)*

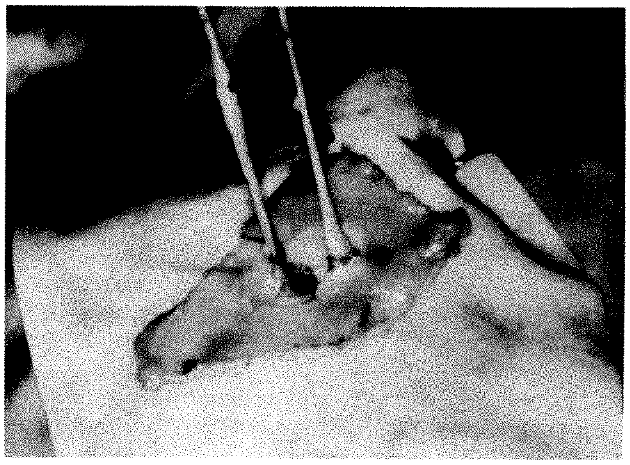

Fig 3. Two saphenous vein grafts are attached to a xenopericardium patch.

grafts are preferable. When saphenous vein grafts are used, proximal anastomosis is problematical as the calcified aorta disturbs its fine sutures. Ostioplasty of the left coronary ostium using a pericardial or venous patch has been reported [2, 3], although in Takayasu's disease heavy calcification may disturb the insertion of a patch around the coronary ostium. If there is no suitable place on the ascending aorta for proximal anastomosis or ostioplasty, insertion of a prosthetic artificial patch [1, 4] or an autopericardial or xenopericardial patch [5] should be considered. We prefer pericardium to prosthetic artificial graft as a patch material. The advantages of a pericardial patch are its easy handling characteristics and its impermeability to blood [6]. This method can avoid the risk of recurrence of ostial stenosis after spread of an inflammatory disease to the site of proximal anastomosis. However, adequate follow-up is necessary on this patient, because the glutaraldehyde-preserved xenopericardium may undergo calcification.

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Placement of a Greenfield Filter in the Superior Vena Cava

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A 75-year-old man with a Greenfield filter in the inferior vena cava for previous pulmonary emboli had recurrent pulmonary emboli. He was unable to take anticoagulants due to gastric ulcer disease. Contrast studies revealed a large thrombus in the left brachiocephalic vein. A Greenfield filter was placed in the superior vena cava through the right internal jugular vein using the femoral insertion apparatus.

(Ann Thorac Surg 1992;53:896–7)

Superior vena caval placement of the Greenfield filter in humans has rarely been performed [1, 2]. We report a patient with clinically significant pulmonary emboli from a large thrombus located in the left brachiocephalic vein. The patient was unable to take anticoagulants due to chronic gastric ulcer disease and a history of gastrointestinal bleeding.

A 75-year-old man with chronic obstructive pulmonary disease had severe shortness of breath and chest pain. He had also had recurrent upper gastrointestinal bleeding from gastric ulcer disease. Two years previous to this admission, a Greenfield filter was placed in the inferior vena cava for pulmonary emboli and concomitant gastrointestinal bleeding. At that time, a ventilation-perfusion scan was strongly positive for pulmonary emboli. Pulmonary arteriography and inferior vena cavography were not performed at that time.

Review of the old operative records revealed that the surgeon intentionally placed the Greenfield filter just superior to the bifurcation of the iliac veins. No reason was given for placing the filter in that position.

Upon this admission, a ventilation-perfusion scan was indeterminate and nondiagnostic for pulmonary emboli. Arterial blood gases revealed severe hypoxemia with an oxygen tension of 38 mm Hg. The patient also had hemoccult-positive stools at this time.

Administration of low molecular weight dextran (40,000 daltons) was begun as well as intravenous fluids and oxygen therapy.

Owing to the previous history of pulmonary emboli and severe hypoxemia, full contrast studies were undertaken. These studies demonstrated a large thrombus in the left brachiocephalic vein (Fig 1). No thrombus was identified in or near the original filter or in the iliac veins. A large venous tributary was noted to enter the inferior vena cava superior to the filter (Fig 2). Pulmonary arteriography was performed, which demonstrated multiple perfusion defects involving both lungs diffusely and intraluminal clot in the pulmonary artery to the right lower lobe. Physical examination as well as ultrasound studies of the lower legs did not demonstrate any evidence of deep venous thrombosis.

The decision for superior vena caval placement of the filter was made owing to the patient's inability to tolerate anticoagulants, the presence of marginal pulmonary reserve, and the fact that the thrombus in the left brachio-

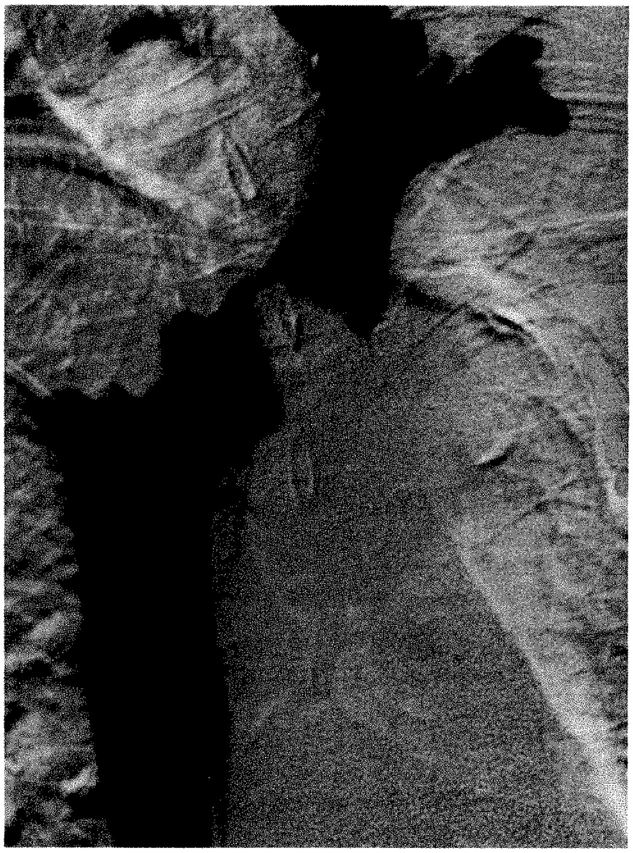

Fig 1. Thrombus in left brachiocephalic vein.

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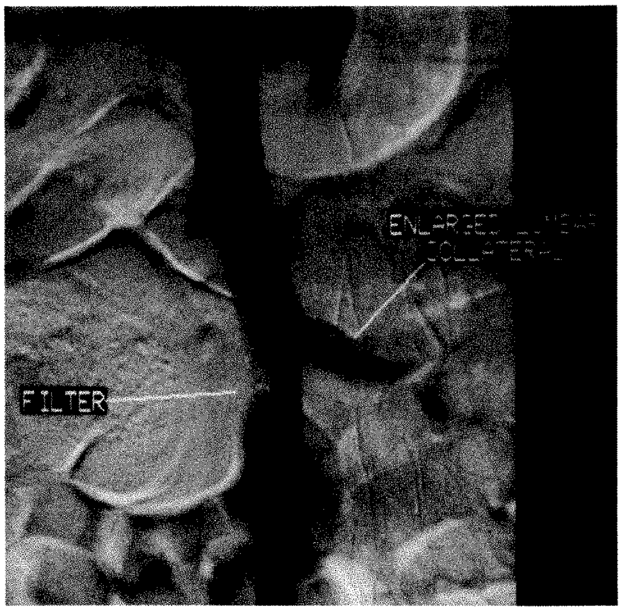

Fig 2. Inferior vena cavogram demonstrating previously placed vena caval filter and large venous tributary entering the vena cava superior to that filter.

cephalic vein appeared to be the only source of embolism. The decision was also made to place another filter in the inferior vena cava superior to the venous tributary to try and exclude this as a source of clinically significant pulmonary emboli in the future.

Using local anesthesia of 1% lidocaine, we isolated the right internal jugular vein at the site of the previous filter insertion. A jugular approach Greenfield apparatus was used to place another filter in the infrarenal vena cava superior to the venous tributary. A femoral insertion device was then used through the same site in the internal jugular vein to place a filter in the superior vena cava between the right atrium and the azygos vein (Fig 3). Position was confirmed by dye injection before placement of the superior vena cava filter.

One-year follow-up reveals no new pulmonary emboli or complaints of upper arm or facial edema.

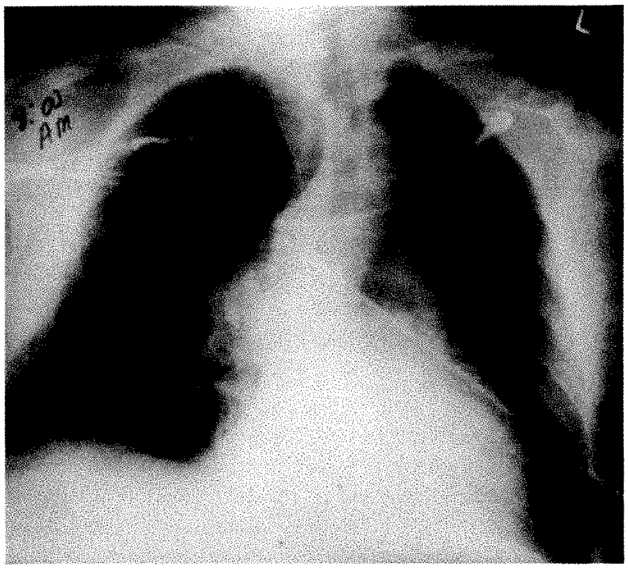

Fig 3. Postoperative roentgenogram demonstrating filter in the superior vena cava.

Comment

The subclavian and brachiocephalic veins may pose a great hazard as a source of clinically significant pulmonary emboli as demonstrated herein. Although superior vena caval filter placement has been described in only 3 patients, experimental studies demonstrate that it is well tolerated in the dog [3]. Although rarely used in humans, superior vena caval placement of the Greenfield filter can be extremely useful in select patients.

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Aortoventriculoplasty in the Management of an Infected Cabrol Graft

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This report describes use of a modified aortoventriculoplasty (Konno procedure) for reoperation on a patient with prosthetic aortic valve conduit endocarditis. The modified Konno procedure was necessary to expose the mid-left ventricular outflow tract to reconstruct an aortic annulus.

(Ann Thorac Surg 1992;53:898–900)

A 62-year-old man who had a repair of type A aortic dissection using a 23-mm St. Jude aortic valve conduit and a 10-mm coronary-Dacron graft anastomosis (Cabrol procedure) was seen a year later with a 1-month history of low-grade fever, indolent pneumonia, and an episode of syncope. Identification of β-hemolytic *Streptococcus* group B from the bloodstream confirmed the diagnosis of endocarditis, and intravenous vancomycin and gentamicin produced immediate defervescence. A previous transthoracic echocardiogram suggested mild aortic regurgitation with no evidence of vegetation or thrombus on the valve. On admission, however, an echogenic mass adjacent to the aorta, a trace of aortic regurgitation, and moderately decreased left ventricular function were observed. An echocardiogram performed 5 weeks into the course of antibiotic therapy showed "rocking" of the ring of the valve conduit, moderate mitral regurgitation, aortic regurgitation, and acute deterioration of left ventricular function consistent with clinical findings of progressive heart failure. An emergency cardiac catheterization confirmed the presence of a large pseudoaneurysm in the mediastinum communicating with the supravalvular section of the aortic conduit and dehiscence of the aortic valve ring. Intraoperative transesophageal echocardiogram (Fig 1) showed the aortic valve conduit floating in the lumen of the pseudoaneurysm.

The patient was placed on femorofemoral bypass with a Biomedicus pump (Biomedicus, Minneapolis, MN) interposed in the venous return circuit to achieve greater flow rates and to facilitate entry and dissection of the mediastinum. A second venous cannula was placed in the right atrium and connected to the venous return circuit for improved drainage. The operation was performed using moderate systemic hypothermia (25°C) and cold blood cardioplegia. The cross-clamp was applied to the distal portion of the Dacron graft just proximal to the innominate artery. Dissection revealed a large perigraft pseudoaneurysm extending into the dome of the left atrium and distal left ventricular outflow tract (LVOT). Erosion of the annular and subannular tissue was associated with aortomitral discontinuity and multiple small nonpenetrating abscess cavities. There was partial dehiscence of the coronary conduit and separation of the sewing ring of the St. Jude prosthesis from the aortic root.

Access to the LVOT for placement of a new valve conduit was obtained by an incision into the right ventricular outflow tract laterally and cephalad to the right coronary ostia (Fig 2). The mitral valve was resuspended with Teflon-pledgeted, interrupted polypropylene sutures (Fig 3). A 2-cm sleeve Dacron graft was sutured to the inferior edge of the sewing ring of a 21-mm St. Jude aortic valve conduit. This sleeve was then sutured to the midportion of the LVOT at the level of the mitral valve, and the distal end of the conduit was attached to the residual aortic arch graft. A 10-mm Dacron graft was anastomosed to the stump of the left and right coronary ostia and attached in a side-to-side fashion to the valve conduit. The right ventricular outflow tract was closed using 3-0 polypropylene mattress sutures with Teflon pledgets (Fig 4). The patient was weaned from cardiopulmonary bypass with the aid of atrioventricular sequential pacing and intraaortic balloon pump counterpulsation, which was discontinued on the second postoperative day. He was discharged home after 2½ weeks of uneventful recovery in sinus rhythm and on lifelong suppressive antibiotic therapy. The patient was seen for follow-up at 1 and 4 weeks and at 6 months postoperatively and has been recovering uneventfully.

Comment

This case report presents a patient 1 year after repair of a type A aortic dissection using a Cabrol procedure [1] who had a complicated valve conduit dehiscence with a large mediastinal abscess secondary to β-hemolytic *Streptococcus* endocarditis.

Christian Cabrol reported 212 Cabrol procedures with

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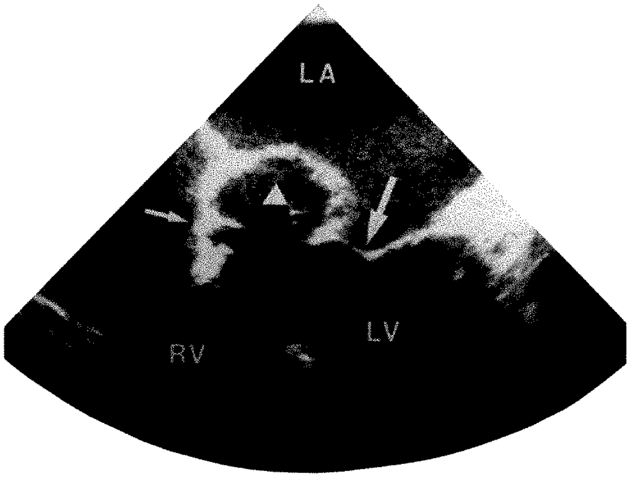

Fig 1. Intraoperative transesophageal echocardiogram demonstrating the pseudoaneurysm bulging into the left atrium. The edge of the aortic valve prosthesis (small arrow) *is separated from the left ventricular outflow tract.* (LA = *left atrium;* LV = *left ventricle;* RV = *right ventricle;* ▲ = *pseudoaneurysm;* large arrow = *mitral valve.*)

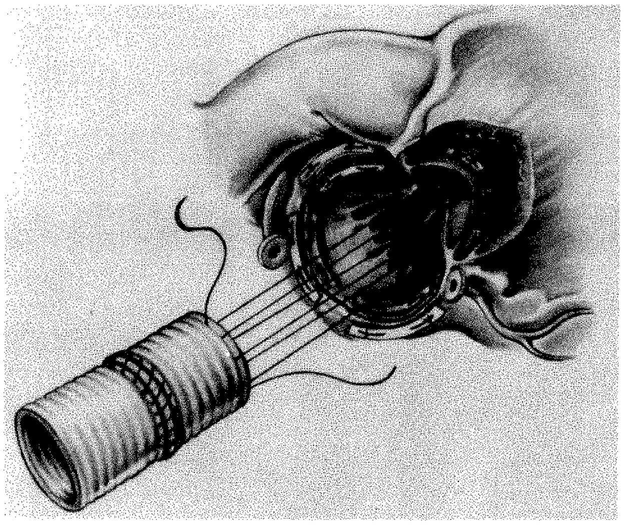

Fig 3. The mitral valve is resuspended and the abscess cavity is obliterated with the pledgeted mattress stitches. The aortic valve conduit with 2-cm sleeve is sutured to the mid-left ventricular outflow tract.

one fatal episode of prosthetic valve endocarditis (Cabrol C; personal communication, 1990). Miller [2] reported one infected Cabrol graft, which was replaced by an aortic homograft. To facilitate reoperation on this group of patients, Cabrol has recommended, and routinely uses, a 1.5-cm to 2-cm Dacron "sleeve" below the valve conduit sutured to the LVOT. This makes de novo implantation of composite grafts and reoperation much easier. In this particular patient, a modified aortoventriculoplasty was used to gain exposure to the LVOT to facilitate the repair of aortomitral discontinuity, obliteration of abscess cavities, and insertion of a valve conduit in the mid-LVOT. The Konno procedure [3, 4] was described to widen the aortic root in children to increase the size of the aortic annulus. It has been used for "tunnel" subaortic stenosis and during adult aortic valve replacement to facilitate implantation of larger prostheses. Where definition of the subannular aortic anatomy is very difficult, access to that area is simplified by the right ventriculoplasty as described in this report. Under most circumstances, patch repair of the right ventricular outflow tract is required to enable closure of the right ventricle and the aorta, but it was unnecessary in this patient.

Reoperation for active prosthetic valve endocarditis carries a mortality rate approaching 60% as compared with 8% to 10% while in the healed phase [2]. Hence, in the case of healed prosthetic valve endocarditis where operation need not be performed immediately, serial echocardiograms [5] can help determine the optimum time of operation by detecting early pathological changes before they become hemodynamically and clinically significant prior to completion of a course of antibiotic therapy.

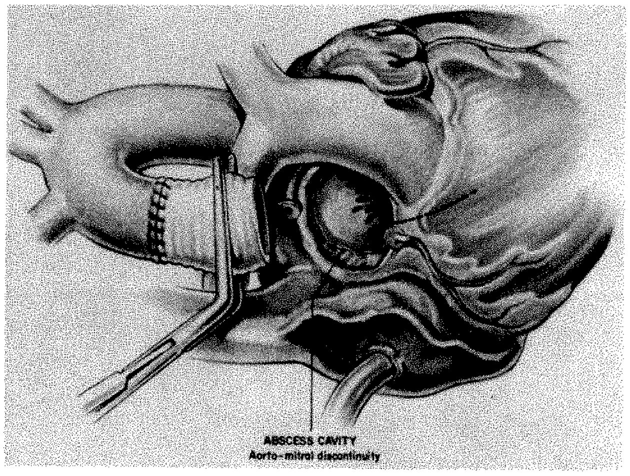

Fig 2. Aortomitral discontinuity; the circumferential abscess cavity and the incision through the right ventricular outflow tract are shown.

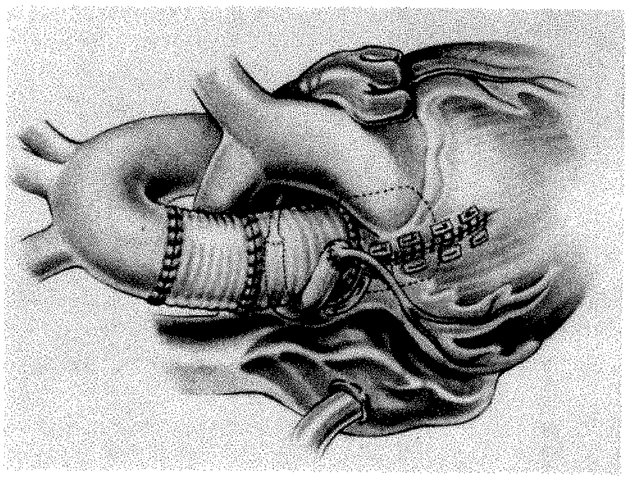

Fig 4. The aortic valve conduit and the Cabrol limb are in place. The position of the 2-cm sleeve in the mid-left ventricular outflow tract is shown.

Another alternative is the use of an allograft as a composite replacement. There is a theoretical advantage to the allograft, in that it may be more resistant to infection than a totally prosthetic conduit in a potentially infected field [6]. The allograft may prove to be the graft of choice when it is readily available.

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False Aneurysm as a Late Complication of Division of a Patent Ductus Arteriosus

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A 58-year-old male patient who had a huge false aneurysm as a late sequela of division of patent ductus arteriosus was surgically managed with success. It is noteworthy that 24 years had elapsed from the initial operation until recognition of the aneurysm. The pathogenesis and method of the surgical treatment are discussed.

(Ann Thorac Surg 1992;53:901–2)

False aneurysm formation is a rare late complication of surgical interruption of a patent ductus arteriosus and is a life-threatening condition. Surgical management is, however, a great challenge. Among 49 hitherto reported cases, only 23 patients (46.9%) have survived operation. This is a case report of a patient with a huge false aneurysm arising from the aortic end of a patent ductus arteriosus divided 24 years before. The wide entrance from the aorta to the aneurysm was successfully closed with Dacron patch aortoplasty.

A 58-year-old man was admitted with a 1-month history of chest discomfort associated with hoarseness and exertional dyspnea. On May 29, 1965, he had undergone division of a patent ductus arteriosus at our institution when he was 34 years old. The ductus had been divided and oversewn with silk sutures. Although massive hemorrhage was encountered during the operation, the postoperative course was uneventful. He was well until November 1988, when he noticed hoarseness. The chest roentogenogram (Fig 1) showed a large abnormal shadow in the left upper mediastinum, which was confirmed to be a false aneurysm by angiography and computed tomography (Fig 2). The pseudoaneurysm had arisen from the aortic end of the divided ductus and caused phrenic and recurrent nerve palsy.

On April 19, 1989, an operation was carried out. Selective endotracheal intubation was instituted, and temporary bypass was established between the right axillary artery and the left external iliac artery. The patient was turned to the right lateral position and the chest was opened through the fourth intercostal space. The proximal and distal portions of the aorta were approached extrapleurally to avoid injuries to the adherent lung. The aneurysm was covered with the upper lobe of the lung, and the adherent lung was untouched during the procedure. After control of the aorta, the aneurysm was incised. A portion of the aneurysm wall was composed of the visceral pleura of the lung. There was no sign of infection. The aortic defect measured 2.0 × 2.6 cm and was located at the site of the aortic end of the divided ductus. The defect was closed with a Dacron patch. During the procedure, distal perfusion was maintained by the temporary bypass graft. Although oozing hemorrhage from the wide raw surfaces mandated rethoracotomy on the next day, the postoperative course was otherwise uneventful. No organisms grew from the removed thrombi.

Comment

Formation of a false aneurysm after ligation of a patent ductus arteriosus was known to surgeons soon after the introduction of this operation [1]. This complication is rare after division, but it does occur [2]. Kazui and associates [3] have reported its incidence as 13.8% after ligation and 0.4% after division. The intervals between the interruption of a patent ductus arteriosus and recognition of a pseudoaneurysm have usually been reported to be less than 1 year. The longest interval thus reported is 11 years [4] but, in that case, the aneurysm was thought to be mycotic in origin. Otherwise, the longest is 9 years [5]. Most authors, therefore, stress the role of infection in the pathogenesis. It is noteworthy that, in the present case, the aneurysm formation was noticed 24 years after the division despite periodic roentgenographic check-ups. Incomplete closure of the ductus, ischemic necrosis of the stump, and degradation of the silk suture may have contributed to the pseudoaneurysm formation in this case.

Operative mortality for this condition has been formidably high [6]. Various assisting measures have been employed such as total or partial cardiopulmonary bypass and circulatory arrest under hypothermia. We routinely use the temporary bypass method without heparinization for thoracic aortic aneurysm repair. Two grafts were individually anastomosed to the right axillary artery and the left external iliac artery while the patients was supine. They were temporary buried under the skin, and after the patient was turned to the lateral position, they were united to be the temporary bypass graft. With the temporary bypass established before thoracotomy, aortic cross-

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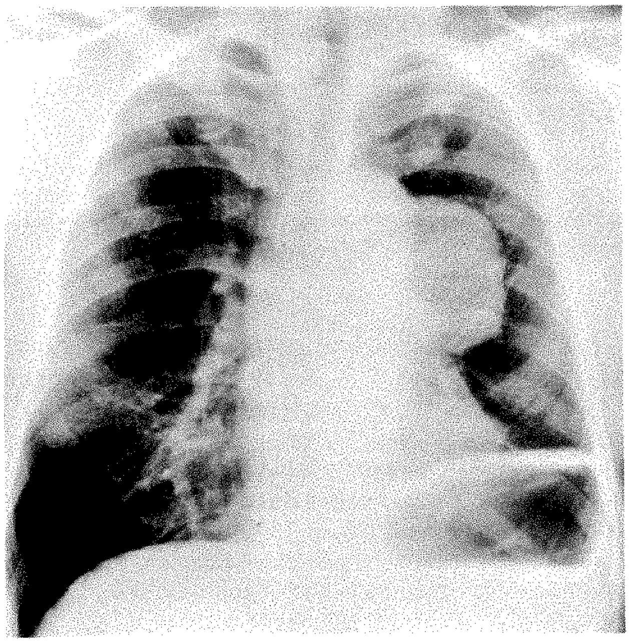

Fig 1. Chest roentgenogram: note the huge aneurysm and elevation of the left diaphragm showing phrenic nerve palsy.

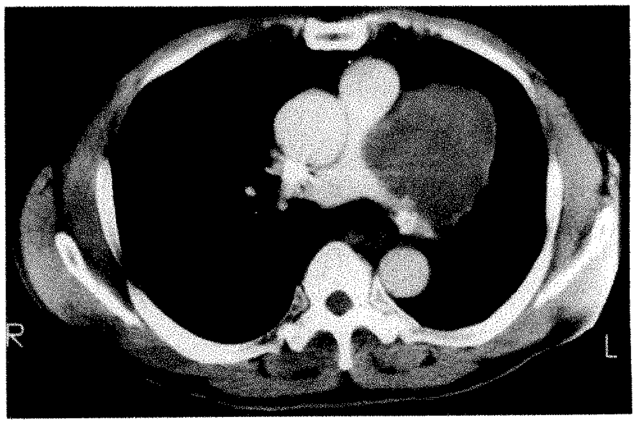

Fig 2. Computed tomographic scan: note the aneurysm, 10 cm in diameter, compressing the pulmonary artery.

clamping can be safely accomplished if rupture should occur during dissection.

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Pancoast Syndrome: An Unusual Complication of Pulmonary Infection by *Staphylococcus aureus*

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Pancoast syndrome, which comprises a lower brachial plexus lesion and Horner's syndrome, usually results from local invasion beyond the confines of the lung by an apical lung carcinoma. Other causes are rare. We report the unusual occurrence of a case of Pancoast syndrome caused by a destructive sclerosing fibrosis after pulmonary *Staphylococcus aureus* infection.

(Ann Thorac Surg 1992;53:903–4)

A 41-year-old woman was admitted to the Orthopaedic Out-Patient Department in Inverness giving a 3-day history of acute onset of interscapular and neck pain with marked restriction of neck movement. There was no history of trauma and the patient was a nonsmoker with right side dominance. On examination, the neck was rigid with tenderness over the lower cervical and upper thoracic vertebrae and the right trapezius. Neck movement was limited due to muscle spasm but right shoulder movement was full. There was weakness (grade III to IV) of the intrinsic muscles of her right hand, but no other neurological deficit was noted.

Over the next 2 days the pain progressed to radiate down the medial border of the right arm with paresthesia in the right hand. Writing and gripping had become difficult. Outpatient treatment comprising analgesics, nonsteroidal antiinflammatory drugs (diclofenac sodium), and a cervical collar was commenced for a presumed diagnosis of prolapsed cervical disc. Two weeks later, the neck pain was now more severe and was exacerbated by movement. The neurological deficits persisted, and in addition she had a small right pupil which was nonreactive to light.

Laboratory investigations revealed a raised erythrocyte sedimentation rate on three consecutive occasions (80 to 110 mm in the first hour), but other hematological indices were normal. Serum electrophoresis and tests for antinuclear antibodies, rheumatoid factor, and Bence-Jones protein were all negative, and she remained afebrile.

A chest radiograph (Fig 1) revealed a right apical opacity, confirmed by computed tomography as a right apical lung mass extending into the root of the neck. Isotope bone scan showed radionuclide uptake in the first thoracic vertebra and first right rib. Sputum cultures were negative. Although a nonsmoker, the patient was suspected of having an apical bronchogenic carcinoma, but percutaneous fine-needle aspiration biopsy under radiological screening produced inflammatory cells only, predominantly neutrophil polymorphs. There was no evidence of malignancy. The patient was transferred to the Thoracic Surgical Unit at Aberdeen Royal Infirmary where a repeat fine-needle aspiration again showed inflammatory cells only.

Exploration through a high parascapular thoracotomy revealed an intense fibrotic reaction confined to the apical segment of the right upper lobe with extrapleural fibrosis and an extrapleural abscess cavity. Culture of tissue revealed a profuse growth of *Staphylococcus aureus.* Histological examination showed an intense extrapleural fibrotic reaction with cellular and focally hyalinizing fibroconnective tissue obliterating the pleural space, replacing chest wall skeletal muscle and extending septally and interstitially into the apical segment of the right upper lobe. Centrally but outside the lung was an acute abscess cavity. There was no evidence of malignancy.

Treatment was commenced with intravenous flucloxacillin subsequently followed by 2 weeks of oral medication with the same antibiotic. She made a good recovery from operation and at review, 6 months later, the only residual neurological deficits were reduced reflexes in the right arm and a right pupil smaller than the left but reactive to light. A repeat computed tomogram of the chest showed right apical pleural thickening and a small air-filled cavity at the lung apex. There was no evidence of rib destruction or recurrence of the mass lesion.

Comment

Henry Pancoast, a radiologist in Philadelphia, first described the syndrome that bears his name in 1932 [1]. It comprised pain in the axilla and arm, weakness of the intrinsic hand musculature, and ipsilateral Horner's syndrome with radiological evidence of an apical lung lesion with rib erosion. The most common cause of Pancoast syndrome is bronchogenic carcinoma; nonmalignant causes, although rare, are recognized. Pulmonary tuberculosis [2] and hydatid cysts [3] at the thoracic outlet have been reported to produce the syndrome, and fungal infection by *Allescheria boydii* in immunosuppressed patients has been implicated [4]. Our patient had previously

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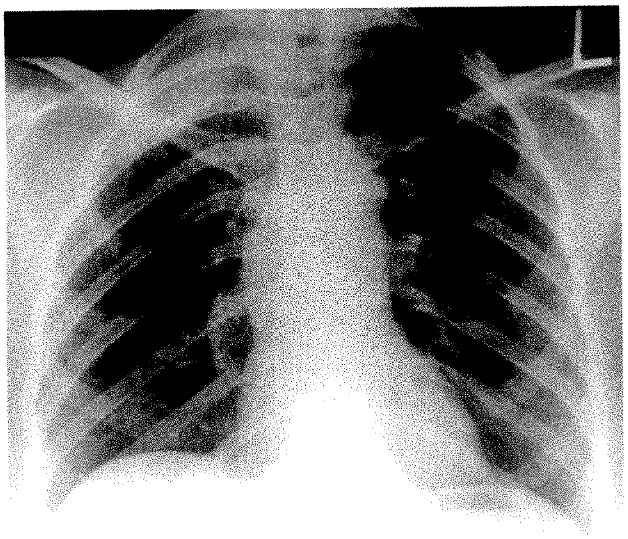

Fig 1. Chest radiograph showing mass at apex of right lung.

been well with no evidence of any of these infections. Nonetheless, they illustrate that inflammatory lesions at the lung apex may cause progressive local damage sufficient to result in Pancoast syndrome.

The anatomical site of the lesion and the profuse growth of *Staphylococcus aureus* from the pus found at operation in our patient implied pulmonary infection by this organism, yet her clinical course was quite unlike a staphylococcal pneumonia. At presentation there was neither history nor clinical evidence suggesting a site of sepsis other than the right lung apex. Histopathologically there was some similarity between the fibrous reaction seen here and that seen in cases of fibrosing mediastinitis/pulmonary hyalinizing granuloma [5]. These conditions are thought to be related to previous tuberculous or *Histoplasma* infection [6] and are known to be progressive, causing tissue destruction. Their pathogenesis is not known but may be related to an atypical immunological response. It seems possible that this case may represent an example of a progressive fibrosing reaction, possibly sharing similar pathogenesis with the above conditions, on this occasion precipitated by infection with *Staphylococcus aureus*.

This case report illustrates a rare but treatable cause of Pancoast syndrome. It highlights that fibrosing reactions at the apex of the lung may cause Pancoast syndrome and reemphasizes the importance of tissue diagnosis in all suspected malignant conditions.

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Leiomyosarcoma of the Pulmonary Artery

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Successful resection of a pulmonary artery leiomyosarcoma was performed in a patient with clinical features of chronic pulmonary embolism. With radical radiotherapy to the mediastinum and solitary right hip metastasis, the patient remained well 6 months later. The difficulty of accurate diagnosis is considered in the light of recent advances in the techniques of cardiac investigation.

(Ann Thorac Surg 1992;53:905–6)

Primary sarcomas of the pulmonary artery are rare tumors [1]. The similarity of the presenting features to those of the more commonly encountered pulmonary thromboembolism means that these tumors are commonly misdiagnosed as chronic pulmonary embolism, with the majority of the tumors reported in the literature being diagnosed at postmortem examination [2]. However, recent advances in echocardiography [3] and angiographic techniques [4] should enable an accurate preoperative diagnosis to be made if this was suspected. With these considerations, we present our recent experience of managing a patient with pulmonary artery sarcoma to review the clinical and radiographic features and the intraoperative and postoperative management.

A 47-year-old woman had a 2-year history of recurrent left-sided pleuritic chest pain and hemoptysis. Repeated ventilation-perfusion scans showed increasingly severe reduction of perfusion to the left lung with normal ventilation such that by the time of her recent admission, the perfusion of the left lung was absent. Despite being on full anticoagulation, she became increasingly incapacitated with breathlessness. She was therefore referred for pulmonary thromboembolectomy. Preoperative angiography (Fig 1) confirmed total blockage of the left main pulmonary artery with extension into the right upper lobar artery. Infusion of streptokinase into the pulmonary artery did not result in any substantial change of the perfusion. Ascending venography revealed no evidence of deep venous thrombosis. There was no previous history of neoplasia, in particular no cervical or uterine malignancy.

At operation through a median sternotomy and with full cardiopulmonary bypass, a hard tumor was found at the bifurcation of the pulmonary artery. The pulmonary artery was opened. The tumor was found to be adherent to the intima, extending into the left main and the right upper lobar arteries. Endarterectomy was performed, with removal of most of the tumor bulk. The pulmonary artery was repaired using polypropylene. At the end of the procedure, the patient was successfully weaned off cardiopulmonary bypass with low-dose dobutamine. Her oxygen saturation, which was poor before bypass, improved postoperatively. After the operation, she made a relatively uneventful recovery.

Histologic examination of the excised specimen confirmed poorly differentiated sarcoma. Immunocytological staining revealed leiomyosarcoma with positive reaction to myosin using antimyocin antibody but negative reaction to cytokeratin, antimembrane antigen, desmin, and vimentin. An isotope bone scan showed increased activity around the right hip. A soft tissue mass was confirmed on computed tomography. Computed tomography-guided needle biopsy of the tumor confirmed leiomyosarcoma similar to that in the pulmonary artery. The patient underwent radical radiotherapy to the mediastinum and the right hip. Radiation esophagitis developed but settled soon after the end of the course. Her dyspnea improved, and thus her exercise tolerance. She remained well with no evidence of recurrence on review 6 months after operation.

Comment

The rarity of pulmonary artery sarcoma means that most cases are initially misdiagnosed as pulmonary thromboembolism with symptoms of dyspnea, chest pain, cough, and hemoptysis [1, 2]. This was demonstrated in this patient. The absence of predisposing factors for pulmonary embolism, persistence of symptoms despite adequate anticoagulation, and the unilateral distribution of massive perfusion defect (which is unusual and is found in less than 1% of patients with documented pulmonary embolic disease [5]) should alert the clinician to the possibility of pulmonary artery tumor. This may be confirmed by two-dimensional echocardiography, computed tomography [3], and angiography [4]. Pulmonary artery sarcomas are readily visualized on angiography [4]. Catheter suction biopsy of the tumor may be successful in obtaining tissue for histological diagnosis [6].

The majority of pulmonary artery leiomyosarcomas were diagnosed at postmortem studies [1], with most of the others found at operation. The delay in the diagnosis and treatment led to development of metastases in most patients, with the majority of metastases to the lungs [7]. Thoracotomy in such patients may carry substantial mortality. Resection usually involved pneumonectomy [3], which may lead to recurrence of the tumor in the remaining lung owing to the proximal location of the tumor.

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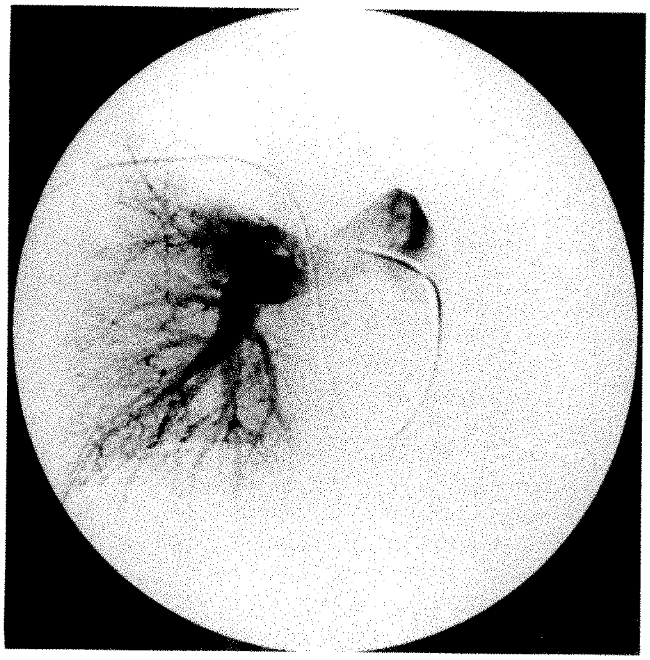

Fig 1. Pulmonary angiogram showing absent perfusion of the left main and right upper lobar pulmonary arteries.

Proximal pulmonary endarterectomy may result in worthwhile palliation [8], as demonstrated here. The average survival after onset of symptoms, however, is less than 12 months [1].

The rarity of these tumors made generalizations about management difficult. Early recognition and therapy may lead to effective palliation and prolonged survival [8].

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Cardiac Surgical Aids: Heart Cup and Stentless Valve Holder

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Département de Chirurgie Cardiovasculaire, CHU de Rangueil, Toulouse, France

We present two new cardiac surgery instruments that we perfected in our department. The heart cup holds the donor's heart vertically within a cold saline solution, thus allowing adequate preparation of the heart for transplantation, as well as the excision of valvular homografts from the recipient's heart. The stentless valve holder is used to hold valvular homografts to ease both their preparation and implantation.

(Ann Thorac Surg 1992;53:907–8)

In this article we present two new cardiac surgery instruments that we perfected in our department.

The Heart Cup

The cardiac graft must be maintained vertically in a cold saline solution in two cases: (1) during donor heart preparation, which consists of dividing the aorta from the pulmonary artery and cutting both of them, removing the left atrium top with an incision meeting up with the four pulmonary veins, and finally incising the right atrium from the anterior side of the inferior vena cava toward the right atrium to avoid the sinus node [1], and (2) during excision of valvular homografts from the recipient's heart. In both these cases, the assistant holds the heart with his or her hands in a vertical position within the cup. This presents two drawbacks: the heart is rewarmed by the assistant's hands, and the assistant cannot use his or her hands efficiently to help the surgeon.

For these reasons, we designed the heart cup. It is a large cup with a support at the bottom onto which are fixed five pliable steel wire fingers looking like a hand. With this instrument the heart is vertically held, fixed, and not rewarmed, and the assistant's hands are free (Fig 1).

This device is atraumatic. We have never noticed any myocardial lesion. In fact, the pressure of the five metallic fingers over the heart is very low because the heart is immersed in a saline solution. Despite this, it is possible to be even more cautious by inserting a compress between the myocardium and the metallic fingers.

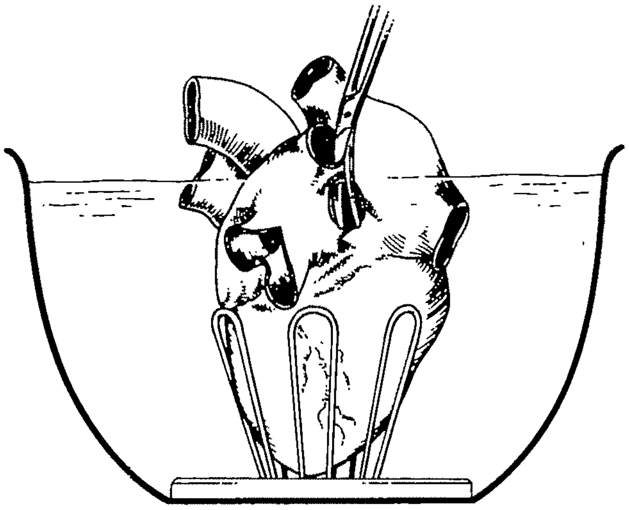

Fig 1. Donor heart in the heart cup. The orifices of the four pulmonary veins are going to be connected.

The Stentless Valve Holder

We designed this holder to ease the surgeon's work during both the preparation and the implantation of stentless valves. These are mainly aortic and pulmonary valvular homografts. They are dissected from the cardiac block. The aortic root must be carefully cleaved from the

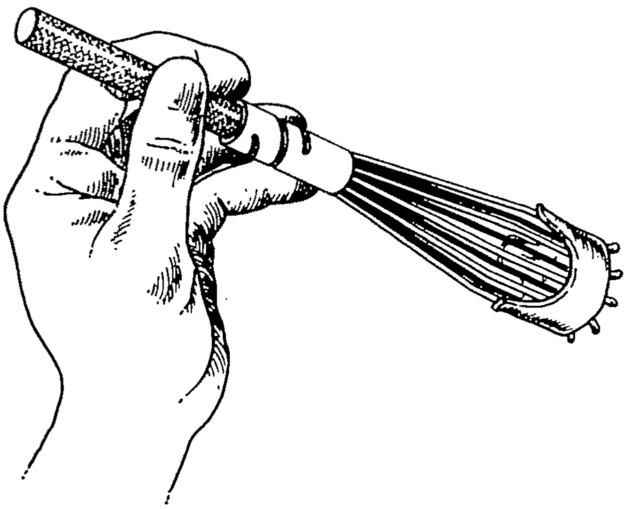

Fig 2. The homograft aortic valve is on the holder, ready for insertion.

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These instruments are patented and manufactured by, and commercially available through, Delacroix Chevalier Instruments de Chirurgie S.A., 13 avenue de la République, 75011 Paris.

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myocardium. This procedure is rather difficult to achieve and requires an assistant's help [2].

Our holder is made of eight elastic steel wires, 18 cm long. They are fixed onto a handle, and their orientation forms a 35-mm circle with a free end. A hard clamp collar with a mirometric screw allows the steel wires to be tightened to 15 mm. Thus, all valve diameters from 15 to 35 mm can be held by this device. Consequently, the valve preparation and implantation are carried out easily and rapidly (Fig 2).

In using this device, we have never encountered any valve trauma. In fact, the steel wires have a very low pressure, which is not exerted on the valve but on the annulus.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1995 may begin the recertification process in 1993. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is May 1, 1993. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Concomitant Repair of Aortopulmonary Window and Interrupted Aortic Arch

Michael T. Ingram, MD, and David A. Ott, MD

Divisions of Surgery, Texas Heart Institute and Texas Children's Hospital, Houston, Texas

Aortopulmonary window with type A interrupted aortic arch was diagnosed in 2 critically ill neonates. Echocardiographic diagnostic methods provided precise anatomic information, which allowed cardiac catheterization to be avoided before operation. Repair was undertaken through a midline sternotomy using hypothermic, low-flow cardiopulmonary bypass with subclavian turndown in one patient and hypothermic circulatory arrest with direct aortoaortic anastomosis in the other. Both methods provided good exposure and allowed favorable anatomic repair.

(Ann Thorac Surg 1992;53:909–11)

Aortopulmonary window accounts for less than 2% of all congenital heart defects. The first repairs of aortopulmonary window were done by using the closed technique. With the advent of cardiopulmonary bypass, repair became much easier. In the presence of other defects, however, aortopulmonary window remains a challenging problem, especially in neonates [1, 2]. We describe 2 cases in which successful concomitant repair of aortopulmonary window with type A interrupted aortic arch was accomplished in neonates after echocardiographic diagnosis.

Case Reports

Patient 1

A 2-day-old boy (3,000 g) was admitted to Texas Children's Hospital. The infant, born after a 40-week gestation, had appeared healthy at birth, but by the end of his first day of life tachypnea and cyanosis developed. Ventilatory support was begun, and after he was given prostaglandin E_1 and small amounts of pressor agents, his condition stabilized.

Echocardiography showed a type A interrupted aortic arch that was distal to the left subclavian artery, aortopulmonary window, and a large patent ductus arteriosus with reverse flow supplying the distal aorta. Because of the infant's deteriorating cardiac function, operation was performed immediately without benefit of cardiac catheterization. Complete repair, rather than a staged procedure, was selected, and the infant was prepared for median sternotomy.

After the chest was opened, a portion of anterior pericardium was excised and preserved in 0.6% glutaraldehyde for use later in the repair. A No. 10 angled arterial cannula was inserted as distal as possible on the ascending aorta. Bicaval 16F venous return lines were placed, and bypass was instituted. The pulmonary arteries were dissected free distally and clamped to prevent overperfusion of the lungs. After the patient was cooled to 26°C, the aorta was cross-clamped and the heart stopped with cold cardioplegic solution, and the cavae were snared with rubber tourniquets. The ventricle was vented through the foramen ovale via a right atriotomy incision and cardiopulmonary bypass flow was reduced to 35 to 40 $mL \cdot kg^{-1} \cdot min^{-1}$. A transverse pericardial patch was fashioned and sewn into place from within the aorta with 6-0 polypropylene suture (Figs 1A, B). The aorta was closed with 5-0 PDS sutures. The aortic arch, descending aorta, and ductus were mobilized. The large ductus was divided and the pulmonary end closed with 6-0 polypropylene sutures (Figs 1C, D). All ductal tissue was excised distally until a good-quality section of descending aorta was reached. The left subclavian artery was divided distally and the distal stump ligated. The proximal end was spatulated and sewn to the descending aorta with 6-0 PDS suture to complete the repair (Fig 1E). The patent foramen ovale was closed primarily, and the patient was warmed and weaned from bypass. Total ischemic time was 29 minutes. An echocardiographic study with Doppler flows 1 month after operation demonstrated good flow in the descending aorta with mild supravalvular aortic stenosis and a patent unobstructed pulmonary trunk.

Patient 2

A 6-day-old male infant was transferred to Texas Children's Hospital with tachypnea and tachycardia. Delivery had been by cesarean section for failure to progress after a normal pregnancy. The diagnosis of interrupted aortic arch with aortopulmonary window was made by echocardiographic study, and the child was treated for congestive heart failure with digoxin, furosemide, and prostaglandin E_1. The patient was electively intubated before operation.

At operation, repair was performed using deep hypothermia to 18°C and circulatory arrest for 23 minutes, during which time the aortopulmonary window was closed with a pericardial patch working through a transverse aortotomy incision with the aortic annula removed

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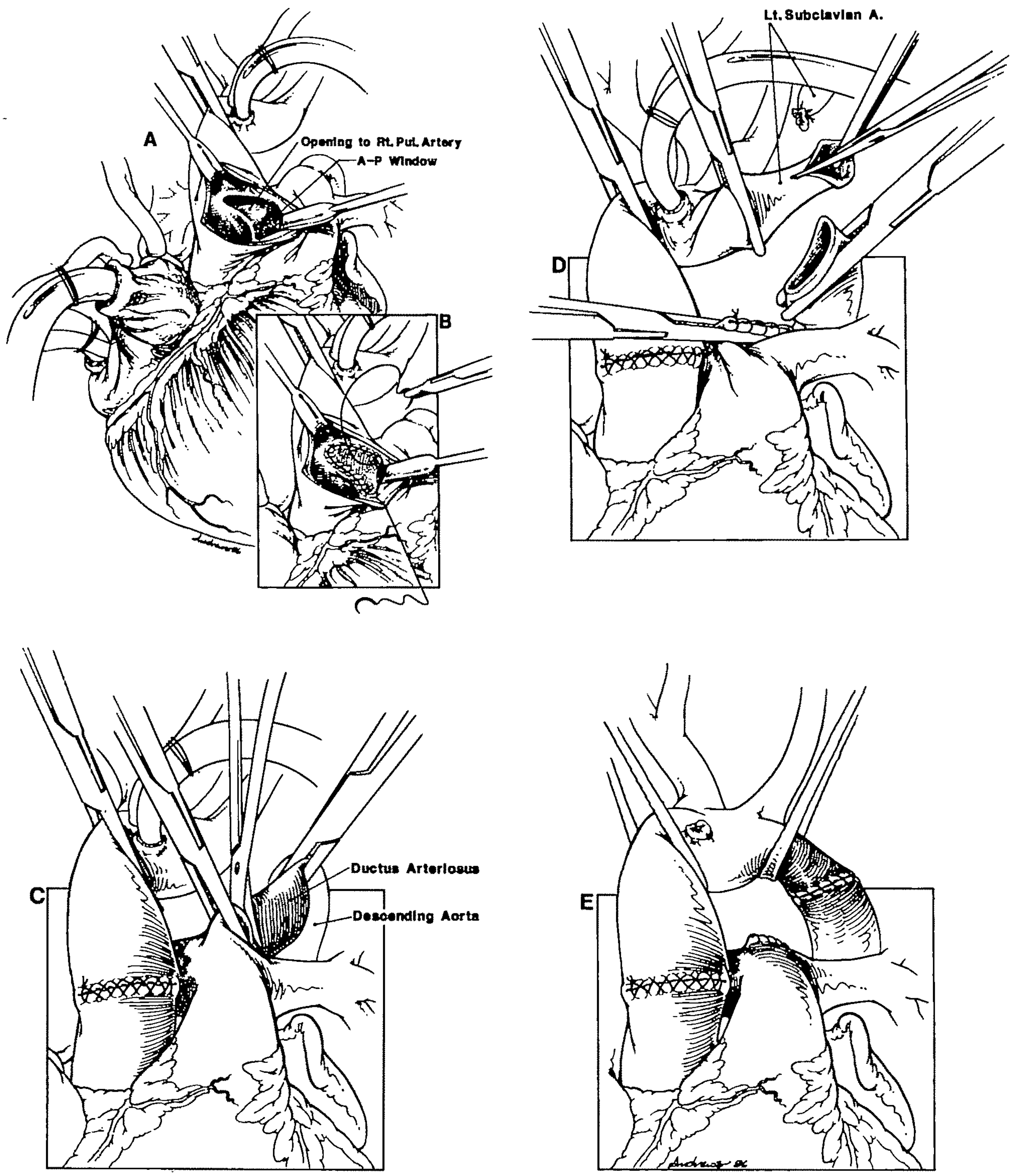

Fig 1. (A, B) Closure of aortopulmonary (A-P) *window with a glutaraldehyde-preserved pericardial patch during hypothermic, low-flow cardiopulmonary bypass. (C–E) Completed repair using the left subclavian artery, sewing down to the descending aorta after division of the ductus.*

and the arch vessels clamped. The descending aorta was mobilized without dividing any branches. The ductus was divided and the pulmonary end oversewn. The aortic end was trimmed until normal descending aorta was exposed, and the distal aorta was anastomosed into the side of the ascending aorta at the takeoff of the left subclavian artery using 6-0 PDS suture (Fig 2). The aortic cannula was then reinserted and the patient warmed and weaned from cardiopulmonary bypass. Total ischemic time was 31 minutes, and pump time was 67 minutes.

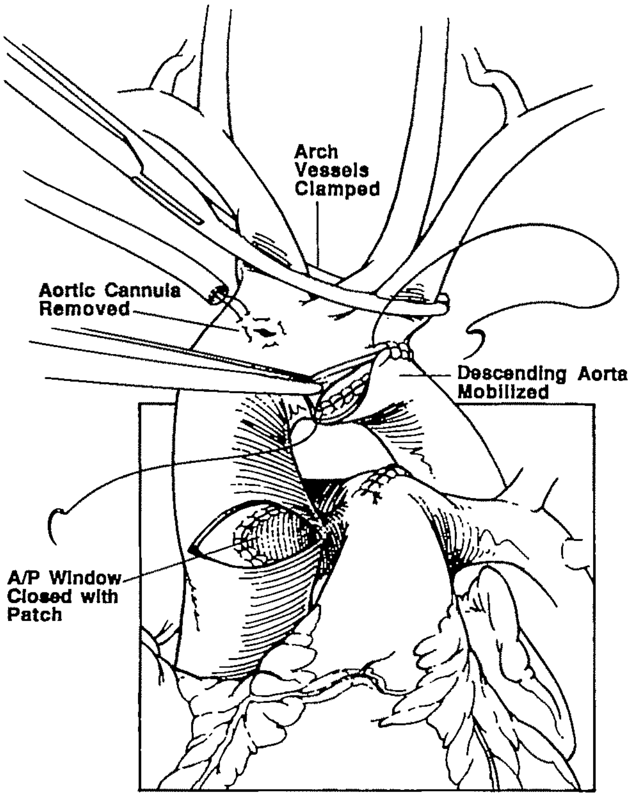

Fig 2. Alternate method of repair using deep hypothermia and circulatory arrest with direct anastomosis of descending aorta to the ascending aorta at the origin of the left subclavian artery. (A/P = aortopulmonary.)

The infant was extubated on postoperative day 3 and discharged 10 days after operation. Four months after operation the child had no echocardiographic evidence of recurrent aortopulmonary window or obstruction to aortic flow. The main pulmonary artery and branches were free of obstruction.

Comment

Other cardiac anomalies (including tetralogy of Fallot, ventricular septal defect, and truncus arteriosus) may coexist with aortopulmonary window. However, the combination of interrupted aortic arch and aortopulmonary window creates a particularly serious surgical challenge because infants with these combined defects are critically ill at birth.

Most reports of the surgical correction of interrupted aortic arch in combination with other lesions, including aortopulmonary window, have described operation on infants rather than neonates, and circulatory arrest has been used for repair. Trusler and associates used circulatory arrest in repairs of type B interrupted arch and ventricular septal defect in a 13-day-old infant [3] and of type B interrupted arch and aortopulmonary window in a 10-month-old infant [4]. A report of 16 patients by Hammon and co-workers [5] reflected increased survival when primary complete repair of interrupted aortic arch was performed.

In our first case we used hypothermic bypass at low flow without circulatory arrest. The turned-down left subclavian artery was of adequate size to reconstruct the descending aorta. In this particular case, primary anastomosis between the descending aorta and aortic arch was inappropriate because it would have created too much tension.

In the second case, however, a primary anastomosis between the distal aortic arch and proximal aorta was possible, although a brief period of circulatory arrest was required for satisfactory completion of the anastomosis.

Cardiac catheterization was considered unnecessary and unduly dangerous in both cases because the important surgical anatomy had been adequately demonstrated by echocardiography, including the aortopulmonary window and the type of interrupted aortic arch. Additionally, echocardiography had ruled out other serious cardiac defects. Echocardiographic diagnostic techniques can provide adequate anatomic information to perform surgical repair of interrupted aortic arch with aortopulmonary window. Appropriate exposure of both defects was provided by the anterior approach through a median sternotomy in these cases. We believe that concomitant repair of both defects using either low flow or circulatory arrest with primary anastomosis or subclavian turn-down is preferable to palliative procedures in these gravely ill neonates. Depending on the individual anatomy a decision can be made regarding whether to use the subclavian turn-down technique, in which case low-flow bypass without circulatory arrest will usually be possible. If it appears that a direct anastomosis will be preferable, a brief period of circulatory arrest with removal of the aortic cannula will be required to obtain adequate exposure for completion of the anastomosis. Closure of the aortopulmonary window is best performed after completion of the arch repair and reinstitution of cardiopulmonary bypass but may be completed during the period of circulatory arrest if technical consideration warrants this approach.

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A Simple Approach to Takedown of a Modified Blalock Shunt

Dominique Metras, MD, Bernard Kreitmann, MD, Alberto Riberi, MD, and Michel Tapia, MD

Children's Hospital "La Timone," Marseille, France

We describe a simple and rapid technique for takedown of right-sided modified Blalock shunts involving a blunt approach between the pericardium and the pleura. We have used this method successfully on either side in 47 cases.

(Ann Thorac Surg 1992;53:912–3)

Takedown of a modified Blalock shunt [1] is a prerequisite to a wide range of corrective procedures. Various approaches can be used. Transpericardial dissection following the pulmonary artery is a usual approach on both sides [2], and the extracardial, transpleural approach can be used for left-sided shunts [3]. We describe a safe, simple, and expeditious approach through the plane of cleavage between the pericardium and pleura. This method has allowed safe shunt takedown in 47 cases including 35 on the right side.

Technique and Patients

After conventional median extrapleural sternotomy, the pericardium is opened longitudinally. After vertical retraction of the pericardium on the shunt side, the plane of cleavage between the pericardium and pleura can be easily located and quickly dissected using a sponge or "peanut." The phrenic nerve, which is easily identifiable, remains adherent to the pericardium (see Fig 1, which shows the right-sided approach). The superior vena cava is then gently lifted to expose the polytetrafluoroethylene shunt. After the fibrous layer encasing the shunt is opened, the shunt can either be occluded using a sturdy clip or divided between two clips or sutures. The approach is the same on the left side except that the superior vena cava is generally absent.

Between 1988 and 1991, we systematically used this approach to take down 35 right-sided and 12 left-sided Blalock shunts (Table 1). No complication was attributed to this step in any of these 47 procedures.

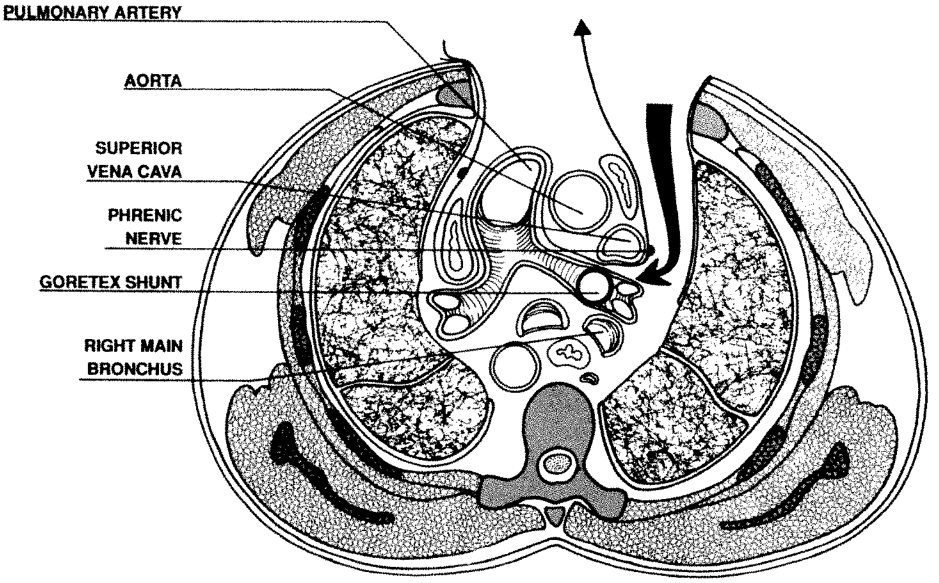

Fig 1. Transverse section of the thorax at the level of the fifth thoracic vertebra showing the approach to a right-sided modified Blalock shunt (arrow).

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Table 1. Diagnoses of Patients Having Takedown of Modified Blalock Shunts

	Modified Blalock Shunt	
Diagnosis	Right-Sided	Left-Sided
Tetralogy of Fallot	9	4
Pulmonary atresia (intact ventricular septum)	10	0
Pulmonary atresia (VSD)	5	3
TGA	6	2
Tricuspid atresia	3	1
Single ventricle	1	1
Corrected TGA	0	1
Total	35	12

TGA = transposition of the great arteries; VSD = ventricular septal defect.

Comment

Shunt takedown before various heart procedures occasionally results in serious iatrogenic complications. The classic approach to right-sided shunts consists in incision of the pericardium and dissection between the aorta and superior vena cava [2]. For left-sided shunts, the usual approach calls for incision of the pericardium and dissection of the left pulmonary artery [2]. The transpericardial approach carries a risk for complications such as phrenic nerve injury, bleeding from mediastinal arteries developed as part of collateralization, damage of the first branches of the pulmonary artery (especially for right-sided shunts), and even damage to the right main bronchus.

A safe alternative with a number of advantages is rapid blunt dissection between the pericardium and pleura. In most cases the pleura is not opened. The phrenic nerve remains adherent to the pericardium and is immediately identified. Once located behind the superior vena cava, the polytetrafluoroethylene shunt can be quickly ligated. If there are adhesions between the cardiac structures and the pericardial sac, unnecessary intrapericardial dissection is avoided, particularly before starting cardiopulmonary bypass. Since we began using this simple and expeditious approach routinely, we have not observed a single complication.

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Intraabdominal Paddle Placement for Internal Defibrillation During Cardiac Reoperation

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Ventricular fibrillation during sternal reentry can be a fatal complication that is vexing to manage when it occurs before complete exposure of the heart. A technique of intraabdominal paddle placement for internal countershock has been used to successfully manage this complication.

(Ann Thorac Surg 1992;53:914–5)

Cardiac reoperations are becoming increasingly common. Sternal reentry carries increased operative morbidity including potential injury to the heart and great vessels, hemorrhage, dysrhythmia, and particularly ventricular fibrillation. Cardiac access can be especially difficult in the repair of congenital cardiac defects when staged or multiple procedures are required and anterior pericardium is absent. Complications often occur early during dissection when lack of exposure and limited access can restrict therapeutic options. The rising use of electrocautery for dissection and hemostasis provokes an increased occurrence of tachyarrhythmias and ventricular fibrillation that require internal countershock, and effective paddle placement can be difficult. Reported herein is a technique that has been used successfully to internally defibrillate patients with a scarred, "frozen" mediastinum during cardiac reoperations.

Technique

A 22-year-old woman had undergone total repair of complete atrioventricular canal defect in infancy. Four months before the current admission, she began to experience symptoms indicative of increasing mitral insufficiency. Echocardiogram revealed 4+ mitral regurgitation, and valve repair or replacement using cardiopulmonary bypass was scheduled. Intraoperatively, extensive thick adhesions were encountered upon opening the sternum. During dissection of the anterior right ventricle, ventricular fibrillation developed. External paddles had not been preapplied, and neither the right nor the left pleural cavity could be entered quickly. One paddle was placed through the peritoneum at the inferior end of the incision. It was held beneath the heart and above the left lobe of the liver, against the diaphragm. The other paddle was placed on the anterior surface of the heart. By doubling the normal energy setting and delivering one electrical countershock of 50 J, we successfully defibrillated the patient. Mitral valve repair was performed, and the patient recovered uneventfully.

Comment

Many methods for electrical countershock during reoperative mediastinal procedures have been proposed. Direct epicardial defibrillation with two internal paddles requires that the heart be extensively exposed before countershock. Appropriate dissection often has not been accomplished at the time of fibrillation, and is sometimes not requisite to the surgical procedure. Use of external paddles requires wide draping of the operative field, possible removal of drapes, and increased chance of contamination [1]. Preapplied electrodes placed outside the operative field have been successful [1–3]. A preapplied posterior intrascapular electrode combined with an anterior internal paddle has also been used [4]. With external countershock, markedly increased energy levels are required, skin burns are common, and success is unpredictable due to varying transthoracic impedance. Transpleural approaches that position the paddles extrapericardially are not applicable when prior internal mammary artery bypass or thoracotomy has been performed. Premature establishment of cardiopulmonary bypass through femoral vessels can be used to manage complications that occur during dissection but adds substantial morbidity compared with a simple countershock.

Peritoneal entry at the inferior aspect of the sternotomy incision allows one internal paddle to be placed immediately above the left lobe of the liver, against the cardiac portion of the diaphragm. With the second paddle on the anterior surface of the right ventricle and a moderate increase in energy settings compared with direct epicardial countershock, defibrillation can be accomplished. Four patients in whom ventricular fibrillation developed after sternal reentry but before cardiac dissection have been successfully managed with the technique. Its advantages include rapid performance and reliable conversion with low energy levels. Energy is delivered directly to the heart without the morbidity of external shocks, and the need for complete cardiac dissection is eliminated, which decreases operative time and blood loss. No complications related to violation of the peritoneal cavity have been encountered.

Intraabdominal defibrillation has been successfully used in pediatric and adult patients who had fibrillation before adequate cardiac exposure during sternal reentry. The technique is proposed as an adjunct for the armamen-

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tarium of the surgeon who performs reoperative cardiac procedures.

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Notice From the American Board of Thoracic Surgery

The part I (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas, TX, on February 7, 1993. The closing date for registration is August 1, 1992.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Charles P. Bailey and Dwight E. Harken—The Dawn of the Modern Era of Mitral Valve Surgery

Lorenzo Gonzalez-Lavin, MD

Marshall University School of Medicine, Huntington, West Virginia

The modern era of mitral valve surgery began in the 1940s. I acknowledge the important contributions of two of our country's outstanding pioneers, Charles P. Bailey and Dwight E. Harken. Their trials and tribulations should encourage future generations of cardiac surgeons to proceed with further developments in this field.

(Ann Thorac Surg 1992;53:916–9)

> Nosotros somos mas por los que fuimos que por lo que somos
>
> Acevedo, 1956

With this philosophical concept that we are what we are regarding our level of development in any field, not only due to our present accomplishments, but owing mainly to those of our predecessors, it is timely to remember the early steps in the evolution of mitral valve surgery. The relevance of this article stems from the fact that the two most outstanding pioneers in the field, Doctors Charles P. Bailey and Dwight E. Harken, will receive a living acknowledgment of their important contributions at the time of this writing. We are indebted to these two pioneers who refused to be hampered by the a priori prediction of imminent failure by some of their colleagues or be stopped by serious obstacles that might hinder their professional lives. These are giants, who with great skill, courage, tenacity, ingenuity, and persistence have allowed us to stand on their shoulders and look further into the horizons of mitral valve surgery.

Surgery for the diseased mitral valve has evolved by leaps and bounds, thanks to a multitude of pioneering surgical efforts. The first suggestion of slightly "notching" the orifice of a stenotic mitral valve was mentioned almost a century ago by D. W. Samways in the *Lancet* in 1898 [1]. From the experimental point of view, the onset of mitral valve surgery can be traced to the beginning of this century, in 1902, when Sir Lauder Brunton wrote the now classic article, "Possibility of Treating Mitral Stenosis by Surgical Methods" [2] (Fig 1). Strong editorial criticism followed [3], which may have dampened the enthusiasm of surgeons at that time. Consequently, the prophetic words of Brunton were unfortunately overlooked for the following two decades.

The first definitive operation on a stenotic mitral valve was performed in Boston by Elliot Cutler on May 20, 1923. Following one of Brunton's suggestions, he inserted a tenotomy knife through the left ventricular wall in an 11-year-old girl and partially divided both mitral valve leaflets [4]. The patient survived for 4½ years, succumbing eventually to mitral regurgitation. At that time, Cutler believed that mitral regurgitation was better tolerated than stenosis and that mitral valve substance should be removed in part. None of the subsequent five operations were found successful [5]. Without wishing to detract from Cutler's historical work, his concept of excising parts of the mitral leaflet probably delayed somewhat the further development of this field in our country.

On the other side of the Atlantic, at the London Hospital, 2 years after Cutler's memorable operation, Sir Henry Souttar performed the first successful finger dilation of a stenotic mitral valve. His patient was markedly improved and lived 5 years . . . "in quite reasonable health, passing away at the end of that time from cerebral embolus arising undoubtedly from the heart . . ." [6]. Why was this most important milestone not followed by a more aggressive approach by the surgeons and cardiologists of that time? The answer was finally disclosed 36 years later, in 1961, when Dwight Harken asked that question of Sir Henry. In a humble letter dated September 22, 1961, Sir Henry's answer was "Although my patient made an uninterrupted recovery the physicians declared that it was all nonsense and in fact that the operation was unjustifiable. In fact it is of no use to be ahead of one's time!" [7]. The physicians did not refer any more patients to him for mitral valve surgery!

The modern era of mitral valve surgery began at the end of the 1940s in Philadelphia with Charles P. Bailey, followed by Dwight E. Harken in Boston. The geographical location of these two colossal pioneers undoubtedly influenced their approach to the mitral valve. Charles Bailey based his approach on Sir Henry Soutar's operation and dedicated most of his efforts to that method. According to the colorful Dr Bailey, while working his way through college, he was a salesman for ladies' girdles. His knowledge of the construction of that garment and its applied garters gave him the basis for better understanding of the anatomy, as well as the treatment of mitral stenosis.

In Boston, Dwight Harken was obviously influenced by the work and experience of Cutler and his admonition to avoid that "tissue thin left atrial wall," while at the same time accepting "selective regurgitation." These concepts encouraged the young Harken to approach the stenotic mitral valve through the left pulmonary vein.

After a substantial amount of work and experimentation with pathological specimens, on June 12, 1946, at the Hahnemann Hospital, Bailey repeated the Souttar proce-

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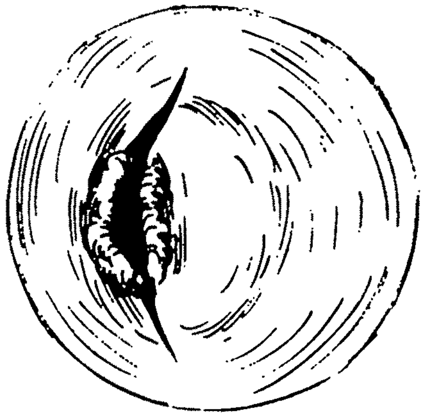

FIG. 402.—"Lengthen the mitral slit." First proposed by Sir Lauder Brunton (1902).

Fig 1. Lengthening of the mitral slit as proposed by Sir Lauder Brunton in 1901 and recounted by Charles P. Bailey. (Reprinted with permission from Bailey CP. Surgery of the heart. London: Henry Kimpton, 1955.)

dure in a nearly moribund woman. The heavily calcified valve was digitally dilated. An initial improvement was followed by sudden death on the second day after operation. On autopsy, considerable restoration of the mitral valve orifice was confirmed; but thrombosis along the lines of splitting had greatly reduced the valve opening. A deliberate enlargement of the stenotic mitral valve at the commissures either by a splitting technique or by cutting with an instrument worn on and guided by the finger was the approach taken by Bailey thereafter [5] (Figs 2, 3).

It was not until June 10, 1948, at the Episcopal Hospital in Philadelphia that Dr Bailey performed the first successful incisional commissurotomy on a 24-year-old woman with severe mitral stenosis [8]. Postoperative clinical auscultatory and radiographic findings were impressive. Dr Bailey decided to present the case at the meeting of the American College of Chest Physicians in Chicago, a thousand miles by rail, 7 days after the successful operation. The patient did well for the next 38 years until respiratory complications following a severe episode of herpes simplex led to her death (Bailey CP, personal communication, October 1990).

The term *commissurotomy* was coined by Thomas M. Durant, Bailey's cardiologist. It describes the separation of fused commissures, and has taken its name from an operation, similar in principle, for the treatment of oral microstomia by plastic surgeons in the past [5] (Fig 4). With increased experience in dealing with the mitral valve, Charles Bailey coined the term *neostrophingic* mobilization to describe the creation of hinges separating the valve by dividing the scar well into the remaining flexible circumorificial tissue. The operative mortality rate reported by him and his associates in 811 cases subjected to mitral commissurotomy without other vascular or septal operation was 8% [5]. Above all, Charles P. Bailey deserves the credit for establishing surgery for the mitral valve on a sound clinical basis.

Dwight Harken became known as a prominent cardiac surgeon during World War II by removing 142 missiles in or in relation to the heart and great vessels [9]. He returned to Boston to a more supportive environment for pioneering work in cardiac surgery. Influenced by Elliot Cutler's doctrine, Harken performed the first direct operation on a stenotic mitral valve on March 22, 1947. Using

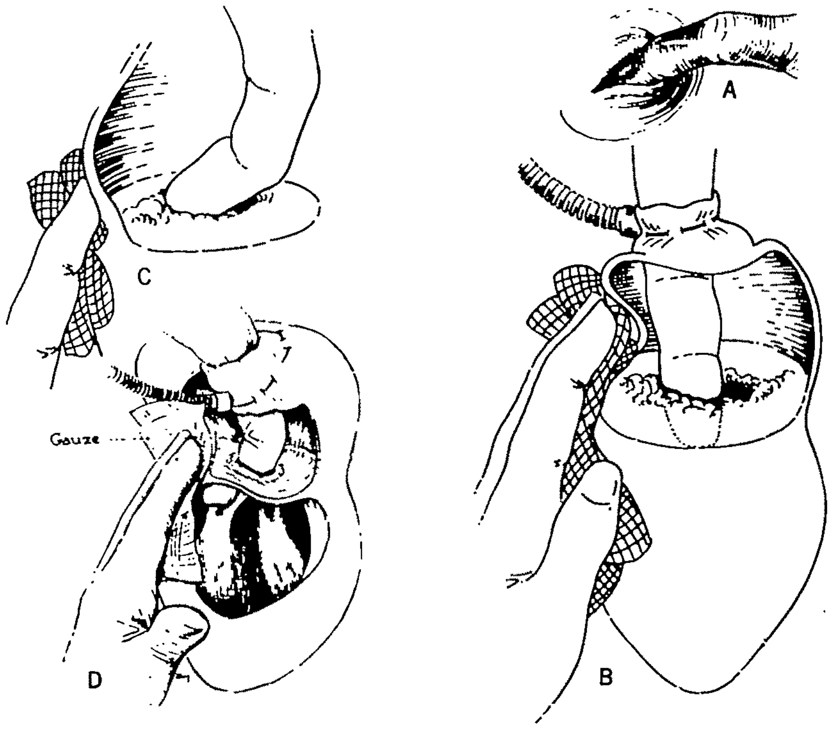

Fig 2. Finger dilation of the mitral valve. (Reprinted with permission from Bailey CP. Surgery of the heart. London: Henry Kimpton, 1955.)

Fig 3. Commissurotomy guillotines used in the early days of closed mitral commissurotomy. (Reprinted with permission from Bailey CP. Surgery of the heart. London: Henry Kimpton, 1955.)

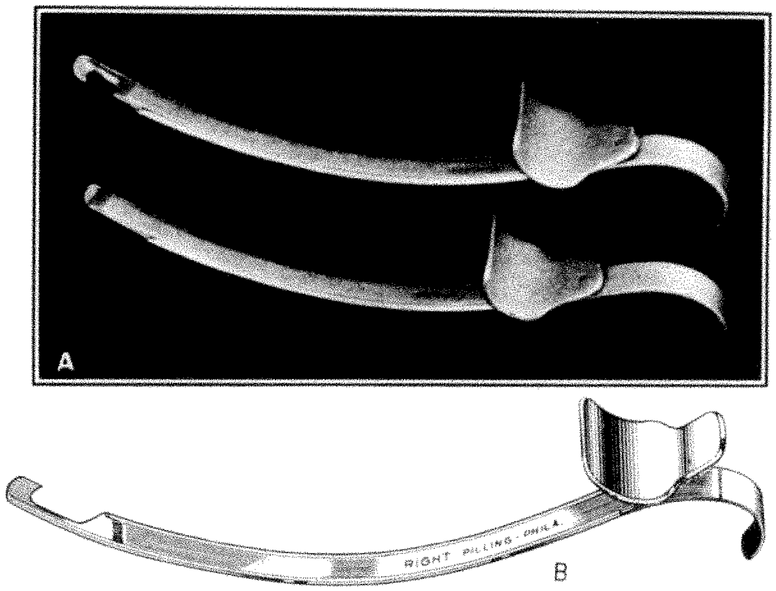

Fig. 417.—**Right and left commissurotomy guillotines, curved-on-the-flat.** *A*, Actual photograph of left-sided instrument. *B*, Drawing of right cutting instrument.

a modification of the Cutler valvulotome, he approached the mitral valve through the left superior pulmonary vein (Fig 5). He excised a portion of the posterior leaflet. Harken clearly described his operation as a "valvuloplasty" and was willing to accept the apparent need for "selective insufficiency" as the price that must be paid for surgical relief of mitral stenosis. Unfortunately, the patient died within 22 hours [7].

According to Dr Harken, he did his first successful direct transatrial approach to the stenotic mitral valve 4 days after Bailey's successful operation. Harken's article was published in November 1948 [10]. Six of Harken's first 10 patients died. This was such a devastating experience that, with the tenth patient and sixth death, Harken thought he would stop doing cardiac operations. It took a convincing friend, Dr Laurence Brewster Ellis, to dissipate the self doubts of the young Harken and induce him to go back to the operating room to continue his pioneering efforts. He then lost only 1 of the next 15 patients! [7].

Fig 4. Surgical concept for the treatment of mitral stenosis based on the plastic procedures used in microstomia. (Reprinted with permission from Bailey CP. Surgery of the heart. London: Henry Kimpton, 1955.)

SURGICAL CONCEPTS OF MITRAL STENOSIS

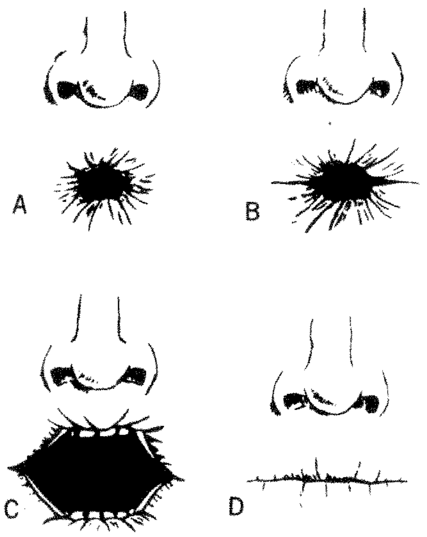

Fig. 393.—**Microstomia, a condition which has been treated for over fifty years by commissurotomy.** *A*, Pathological state. *B*, Incision of commissures (plus suture approximation of mucous and cutaneous surfaces). *C*, End result—mouth open. *D*, End result—mouth closed. Note the functional restoration and absence of dribbling (incompetence).

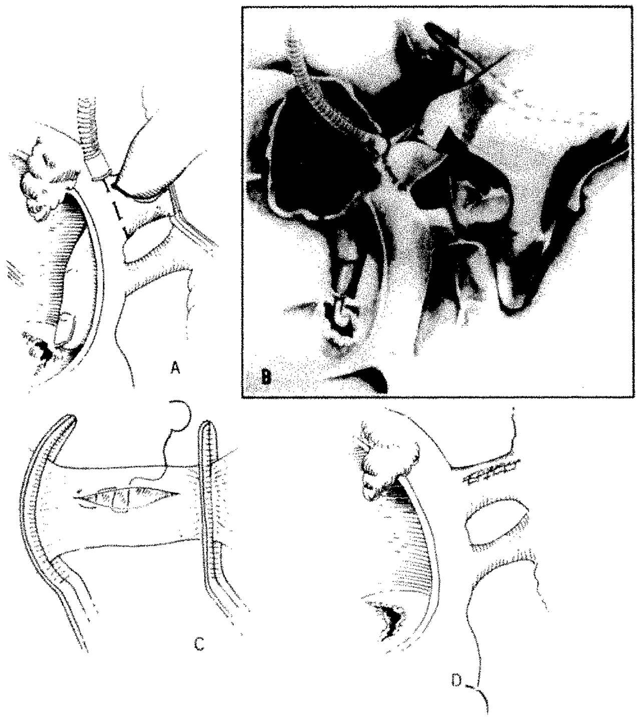

Fig 5. Surgical approach to the mitral valve through the left pulmonary vein. (Reprinted with permission from Bailey CP. Surgery of the heart. London: Henry Kimpton, 1955.)

In closing I quote Doctor Acevedo, my first clinical mentor, who used to say, "We owe our present level of development more to the accomplishments of our predecessors than to those of our own. However, we must continue to strive, as our ancestors did, for newer achievements." In doing so, ours and future generations of cardiac surgeons will have a secure and solid basis from which to embark.

I thank Ms Sarah Noecker for reviewing the manuscript and Ms Kim Damron for typing the manuscript.

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Replacement of the Thoracic Aorta With Intraluminal Sutureless Prosthesis

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A survey of the collective experience reveals that between 1976 and 1990, a sutureless intraluminal prosthesis was used to replace the ascending thoracic aorta, arch, and descending thoracic aorta in 122, 14, and 81 patients, respectively. During these 217 operations, at least 364 of the 434 anastomoses were performed by sutureless fixation. The underlying disease processes consisted of acute and chronic dissections; atherosclerotic, Marfan's, and mycotic aneurysms; and intraoperative disruptions of the ascending aorta. The data in the literature suggest that sutureless fixation shortens aortic cross-clamp time and reduces blood loss. Early graft-related complications were few and probably can be further reduced by improving surgical techniques. The incidence of paraplegia and renal failure after descending aortic grafting was identical at 2.5%. The operative mortality rate for ascending aortic, arch, and descending aortic replacement was 13.1%, 42.9%, and 14.8%, respectively. Long-term follow-up of 143 patients revealed satisfactory graft function with three possible device-related deaths and no other known complications attributable to the prosthesis. There are, however, anecdotal references to late complications from the intraluminal prosthesis. Most of these relate to faulty implantation techniques, but some could be due to flaws inherent in the concept of sutureless grafting. The collective experience suggests that grafting of the thoracic aorta is less hazardous with the sutureless than with the conventional sutured anastomosis technique. The implications of the anecdotal accounts about late complications remain to be determined.

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Replacement of the thoracic aorta represents a formidable challenge and is associated with a higher mortality and morbidity than most other cardiovascular operations. The increased hazards relate in large part to the problems inherent in the construction of conventional sutured anastomoses between a tubular prosthesis and a diseased aortic wall. The process can require an inordinately long time. The sutures frequently tear the friable aortic tissue and produce massive or even lethal bleeding through the anastomosis. Control of hemorrhage can be difficult and compounds the time-related complications of an extended period of pump-oxygenator support necessary for completion of the grafting. The metabolic and hematologic disturbances associated with prolonged periods of mechanical circulation, the lengthy exposure to myocardial ischemia from aortic cross-clamping, and the large volume of banked blood transfusions are especially harmful in an elderly population with a relatively high incidence of coexisting diseases of vital organ systems.

In an attempt to reduce the risks of aortic replacement operations, an intraluminal sutureless graft was introduced approximately 15 years ago [1, 2]. The new prosthesis is inserted simply with tape ligatures without the need for sutured anastomoses. The early reports [1–3] maintained that the sutureless technique shortens graft insertion time and provides secure fixation with minimal bleeding from the anastomotic site. The fixation ligature also obliterates the false lumen produced by aortic dissection and obviates the need for an additional maneuver to reappose the separated layers of the vessel.

The early experience with the sutureless prosthesis was gratifying and held the promise of reducing the risks associated with aortic grafting [3–5]. It was anticipated that the sutureless technique would be used with gradually increasing frequency and would eventually become a preferred alternative to the suture anastomosis method for replacement of the thoracic aorta. The literature, however, indicates that the newer approach enjoys only modest acceptance and that the conventional method remains the most commonly employed choice. To assess the potential of the sutureless graft in improving the results of thoracic aortic replacement operations, the published experience with the new prosthesis was recalled through a computerized search of the literature, and the pertinent English-language publications [1–25] were reviewed.

Intraluminal Sutureless Graft

The intraluminal sutureless graft consists of a standard low-porosity woven Dacron tubular prosthesis with a grooved, rigid polypropylene fixation spool attached to each end. These terminal solid rings are covered with porous Dacron velour for cushioning the aortic wall under the fixation tapes and for encouraging tissue ingrowth (Fig 1). The rings are radiopaque. The most commonly

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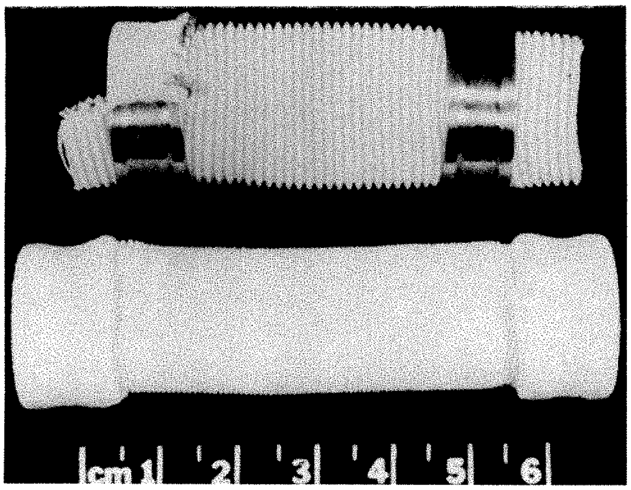

Fig 1. The Bard intraluminal sutureless prosthesis. In the top sample, the covering of the fixation rings has been partially removed.

used graft is commercially available in ten diameters between 18 and 34 mm and in lengths of 4, 6, and 8 cm (USCI intraluminal vascular prosthesis; C.R. Bard, Inc, Billerica, MA). A tapered version with different-sized spools at the two ends, designed to accommodate the disparity between the proximal and distal aortic luminal diameters, is also available. Recently, a variable-length sutureless graft was introduced (Meadox intraaortic grafts; Meadox Medicals, Inc, Oakland, NJ), but the reported experience with this design is limited to 4 patients [21]. This prosthesis is 25 cm long and is commercially available in ten diameters ranging between 18 and 36 mm (Fig 2).

The Bard standard intraluminal graft has been modified by user surgeons in several ways. At times, one of the aortic stumps is not deemed suitable for sutureless fixation, or the disease process in the aorta requires implantation close to a vital branch such as the coronary, innominate, or left subclavian artery, and there is concern that the prosthesis may obstruct the adjacent branch orifice. In these situations, one spool is amputated, and the cut end of the graft is anastomosed to the aorta with the conventional suture technique (modified single-ring graft). The other ring is connected by the ligature fixation method. For simultaneous replacement of the aortic valve and the ascending aorta by the Bentall approach, a cardiac valvular prosthesis is sutured inside the cut end of a modified single-ring graft (composite graft).

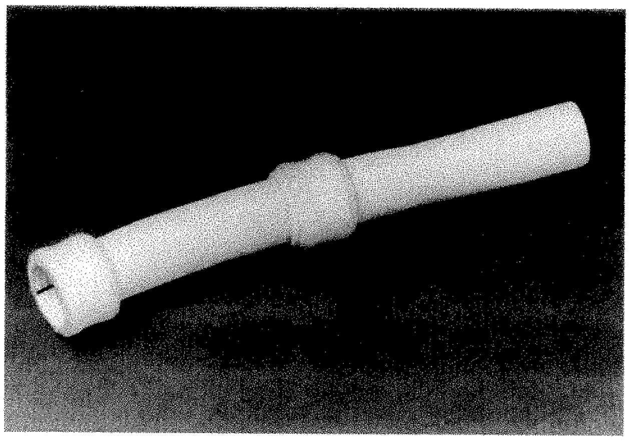

Fig 2. The Meadox variable-length intraluminal sutureless prosthesis. The arrow *points to the movable fixation ring.*

The sutureless device can be lengthened by dividing the body of the graft and either interposing a matching sized tubular prosthesis with suture anastomoses or telescoping a Gore-Tex graft over the rings of two standard intraluminal devices and securing it with tape ligatures (elongated graft). The Meadox variable-length sutureless prosthesis is manufactured with one fixed and one mobile ring. The latter slides along the graft so that it can be adjusted to the desired length simply by moving the ring to the appropriate position on the prosthesis (see Fig 2). Sidearms can be attached to either the Bard or the Meadox prosthesis with end-to-side suture anastomoses (branched graft). Thus, the sutureless prosthesis can be modified for replacing any part of the thoracic aorta, including the arch.

Technique of Insertion

The technical aspects of intraluminal graft insertion have been adequately described in the various reports [1–25]. The basic maneuvers are depicted in Figure 3. For implantation of the prosthesis, a loosely fitting terminal spool is inserted inside the aortic lumen. The tape ligature is tied tightly around the segment of the aorta overlying the deepest point of the groove in the terminal spool. Accurate circumferential placement of the tape is essential for stable fixation. A second tape is tied snugly around the graft and aortic wrap immediately adjacent to the ring. Several reinforcing mattress sutures are placed through the cloth cover of the spool and the adjacent aorta. To prevent occlusion of the coronary ostia by a migrating prosthesis, secure fixation of the proximal ascending aortic anastomosis is especially important. Cannulation of the coronary ostia during construction of the proximal anastomosis provides protection against inadvertent occlusion of the coronary arteries by the prosthesis. Some surgeons recommend that the fixation sites between aorta and graft ring should be wrapped with either a tubular vascular prosthesis or Teflon felt to stabilize the union and to prevent erosion, pseudoaneurysm, or other local complications.

Several technical features deserve emphasis, as failure to adhere to seemingly minor details may result in catastrophic and even lethal complications. A tightly fitting spool may tear the aortic wall; therefore, use of a prosthesis that fits loosely inside the aortic lumen is crucial. Sizing of the aorta is best accomplished intraoperatively with cardiac valve sizers. Selection of a graft one size smaller than indicated by this measurement is recommended. The diameter of the aorta can also be estimated before the operation by measuring the opacified vessel on cut films of the aortogram and subtracting a 30% magnifying factor [18]. The computed tomographic scan pro-

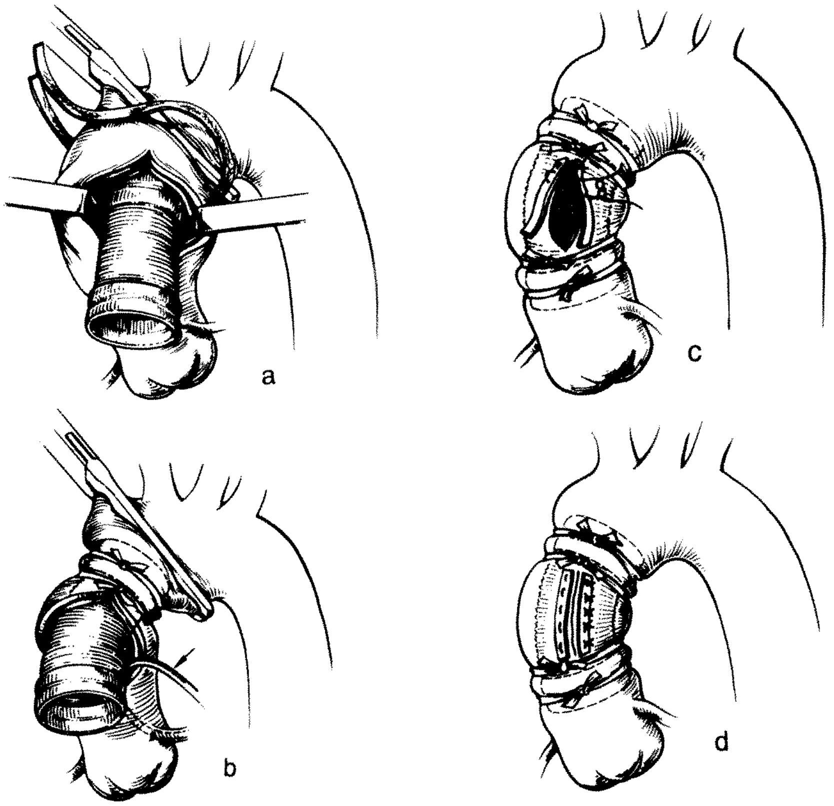

Fig 3. Replacement of the ascending aorta with a Bard sutureless prosthesis. (a) The tape ligature is passed behind the aorta at the distal connection site. The aorta is cross-clamped and opened. The distal spool is introduced into the lumen. (b) The distal fixation ligature is tied. Extreme care is exercised to keep the tape over the deepest point of the concave groove around the entire circumference of the fixation ring. The tape ligature reapproximates the dissected aortic layers and obliterates the false lumen. A cannula is in the left coronary ostium (arrow) *to prevent obstruction by the proximal spool. A second cannula necessary to protect the right coronary artery from obstruction and the stabilizing sutures between the Dacron covering of the spool and the aorta are not shown. (c) The proximal and distal connections are completed. Additional tape ligatures are tied around the aorta and underlying graft immediately adjacent to the terminal spools. Wrapping of the aorta around the graft is started. (d) Wrapping of the graft is completed. The sutures, buttressed with Teflon felt strips, achieve a snug fit.*

vides a more accurate approximation of aortic diameter. An unduly long graft predisposes to kinking, obstruction, thrombosis, and hemolysis. Thus, accurate estimation of the correct length is essential. The external diameter of the fixation ring that fits inside the aortic lumen is 2 to 3 mm larger than the internal opening, and the smaller-sized prostheses may produce an undesirable gradient. Thus, the use of intraluminal grafts in patients with small aortas is not advised [7].

Systemic heparinization has not been employed during replacement of the descending thoracic aorta by several reporting surgeons [7, 8, 25] as well as by our group [3]. Because anticoagulation does not appear to be an absolute requirement, the sutureless technique offers a special advantage during replacement of the descending aorta in patients with multiple organ injuries from trauma. The intraluminal prosthesis can be preclotted.

Experience With Replacement of the Ascending Aorta

Between 1976 and 1990, replacement of the ascending aorta with the intraluminal sutureless prosthesis was reported in 122 patients from 16 institutions (Table 1). The number of procedures at the different centers ranged between 1 and 41. Eleven surgical teams performed less than four operations and five groups, more than five. The underlying disease processes are listed in Table 1. Close to three quarters of the procedures were performed for dissections, and almost all of the others for aneurysmal disease. There were four operations for irreparable intraoperative aortic dissection or disruption during three myocardial revascularization operations and one aortic valve replacement [22, 24, 25]. Patients with Marfan's syndrome were rejected by at least two teams [3, 12] but were accepted by three others without untoward consequences [13, 18, 25]. One third of the patients in whom the initial clinical features were specified were seen with preoperative hypotension, cardiac tamponade, or rupture of the aorta.

The type of Bard sutureless graft used for ascending aortic substitution was specified for 71% of the operations (see Table 1). In the majority, the standard double-ring prosthesis was employed, whereas a modified single-ring graft was used in 19% of the patients. Sutureless grafting was combined with aortic valve replacement or suspen-

Table 1. Ascending Thoracic Aortic Grafting With Sutureless Prosthesis

						Aortic Clamp Time (min)				Operative Mortality			
Disease	No. of Patients	Graft Type	No. of Patients	Associated Procedure	No. of Patients	Procedure	No. of Patients	Mean	Range	Disease	No. of Patients	Deaths	%
Dissection		Standard ±	71	AVR	36	Standard	27	43.9	19–73	Dissection			
Acute	75	Modified ±	16	AV suspension	25	Standard +	14	56.0	19–80	Acute	75	12	16.0
Chronic	13	Unknown	35	CABG	15	Modified +	2	46.5	36–57	Chronic	13	0	0
Aneurysm	30			AVR + MVR	1	Standard	2	88 ± 18		Aneurysm	30	2	6.7
Intraop				MVR + TVP	1	Modified	1			Intraop	4	2	50.0
Dissection	2					Modified +	9						
Disruption	2					Unknown	67						
Total	122		122		78		122	. . .	. . .		122	16	13.1

AVR = aortic valve replacement; AV = aortic valve; CABG = coronary artery bypass grafting; MVR = mitral valve replacement; TVP = tricuspid valvuloplasty; + = with associated procedure; ± = with or without associated procedure.

sion, coronary artery bypass grafting, or multiple-valve procedures in various combinations in 64% of the procedures.

During the 88 operations for ascending aortic dissection, the aortic valve was replaced in at least 9 patients and resuspended in 25 others, and coronary arteries were bypassed in at least 6 patients. For aneurysmal disease, aortic valve replacement and coronary artery bypass grafting were performed more frequently (19/25 and 5/25, respectively).

Only limited information was provided about duration of aortic cross-clamping, and the data did not permit analysis of all relevant variables or length of aortic occlusion in the entire population. The available data were collated and are presented in Table 1. Marked interinstitutional variation was a striking feature of the collective experience. One team [13] required between 19 and 25 minutes of aortic occlusion for standard graft placement in 6 patients, whereas another group [9] reported a mean of 88 ± 18 minutes of aortic clamping for two standard and ten modified single-ring graft implantations combined with aortic valve resuspensions in nine of these operations. In contrast, the last-mentioned team required 111 ± 36 minutes of aortic cross-clamp time during 94 similar procedures in which the conventional suture technique was used. Several authors commented that aortic cross-clamp times decreased with increasing exposure to the procedure.

There was consensus that blood loss was less with the sutureless than with the conventional technique, but quantitative data to support the impression were limited. One group [1] reported less than 500 mL of postoperative tube drainage in each of 4 patients. Reentry for excessive blood loss was necessary in 2 of the 101 patients for whom this information was specified. The bleeding did not originate from sutureless connection sites in either of these two reoperations. In one center [9], death from exsanguination was noted in 1 (8.3%) of 12 patients with a sutureless graft and 16 (17.0%) of 94 patients with a sutured graft. The single fatal hemorrhage in the sutureless group was from the sutured anastomosis of a modified single-ring graft.

The operative mortality rate for sutureless grafting of the ascending aorta in the collective experience was 13.1% (see Table 1). The incidence of a fatal outcome was highest in a small cohort with intraoperative aortic injuries (50%) followed by acute dissection (16.0%) and aneurysmal disease (6.7%). There were no deaths among 13 patients having operation for chronic dissection.

The causes of the 16 deaths associated with ascending aortic grafting varied. Three patients died of exsanguination: 1 from rupture at the level of the aortic cross-clamp, 1 through the conventional suture line of a modified single-ring graft, and 1 from disintegration of the aorta at the tape fixation site. This last patient is the only instance of fatal bleeding from at least 364 sutureless anastomoses in the collective experience. One patient had a fatal postoperative dissection into the left coronary artery and another, into the left carotid artery. The sites of entry into the false lumen were not specified. There were nine lethal myocardial infarctions or heart failures. One of the latter deaths was attributed to occlusion of the right coronary artery by a slipped proximal spool. One patient died of sepsis and 1, of unknown causes.

Experience With Replacement of the Aortic Arch

The aortic arch was replaced with a sutureless prosthesis in 14 patients. There were seven operations for dissections, six for true aneurysms, and one for a false aneurysm. In most of these procedures, separate standard grafts were inserted into the proximal aortic stump and into the distal aortic stump, the adjacent free spools were amputated, and the cut ends were joined by sutures. If the combined length of the two intraluminal grafts was too short, the gap was bridged by interposing either a conventional tubular prosthesis using suture anastomoses or a Gore-Tex graft inserted with the ligature fixation method. On at least one occasion, a conventional graft was sutured to one of the two aortic stumps.

There were 6 operative deaths. One patient died of hemorrhage from a sutured anastomosis, 1 could not be weaned from the pump-oxygenator, and 1 died of a perioperative stroke 196 days after operation [9, 25]. The causes of the other 3 deaths were not disclosed. No complications were attributed to the tape fixation sites or to the sutureless graft itself.

Experience With Replacement of the Descending Aorta

Replacement of the descending thoracic aorta with a sutureless graft was reported from eight institutions in 81 patients (Table 2). Five surgical teams performed fewer than five operations, whereas the other three did 11, 11, and 40 operations. The distribution of the aortic disease processes is listed in Table 2. Acute and chronic dissections constituted a little more than half of the disease processes, followed by degenerative aneurysms, traumatic transections, and mycotic (*Salmonella*) aneurysms, in that order. Approximately two thirds of those patients whose initial conditions were described presented with complicated vascular lesions or compromised, life-threatening hemodynamics (see Table 2).

The lower-body circulation was supported with various forms of cannulation for mechanical pumps or extraanatomical temporary shunts in 30% of the operations, whereas the "clamp and connect" technique without circulatory support was employed in practically all the others (see Table 2). In almost 80% of descending aortic replacements, unmodified two-ring grafts without associated procedures were used (see Table 2).

Aortic cross-clamp times were supplied for more than two thirds of the operations (see Table 2). In the majority, the ischemic period lasted less than 30 minutes and in a sizable number, 10 minutes or less. There were marked variations in aortic cross-clamp times among the different centers. Oz and colleagues [19] implanted 21 standard sutureless grafts during an average aortic cross-clamp time of 9 minutes (range, 4 to 18 minutes) in patients without a previous operation. Another team [9] reported 48 ± 14 minutes of aortic clamping for seven standard and four modified single-ring graft implantations. In contrast, this same group required 85 ± 41 minutes for replacement of the descending thoracic aorta by the suture technique in 35 patients.

Statements about reduced intraoperative blood loss were made in several reports, but quantitative data to support the claim were provided from only two series. One team [7] reported that during two operations, 600 mL and 800 mL of blood were lost. In another center [19], an average of 4 units of banked and autologous blood was required in 25 operations. Five patients needed no blood transfusions; 12 received between 1 unit and 4 units of blood; 6, between 6 and 9 units; and 2, between 10 and 20 units of blood. In a third institution [9], fatal hemorrhage was encountered in none of 11 patients operated on with the sutureless grafting technique and in 4 of 35 patients operated on with the suture anastomosis technique. In the collective experience, the mediastinum was explored for excessive bleeding in four of the 71 sutureless replacement operations for which this information was specified. The fixation site was not the source of bleeding in any of the 4 patients.

There were two instances of paraplegia (2.5%) and two cases of nonocclusive renal failure (2.5%) among the 81 patients. All four ischemia-related complications were encountered in patients whose lower-body circulation was supported with some form of mechanical perfusion system and occurred in a series with longer aortic cross-clamp times. Lemole's team [19] used the "clamp and connect" technique exclusively in 40 operations without seeing the complications of renal failure and paraplegia. Early spool dislodgment requiring reoperation and repositioning was observed in two instances [19, 25]. Both patients survived the corrective operation, but 1 died 6 months later of sepsis from a pleural empyema [19]. Graft thrombosis occurred in 2 patients, both of whom died [25].

The operative mortality for replacement of the descending thoracic aorta with a sutureless graft was 14.8% (see Table 2). The available data did not allow separation of deaths of patients with acute and chronic aortic dissections. The incidence of a fatal outcome was higher for dissections than for degenerative aneurysms (8/43, 18.6%, versus 3/29, 10.3%). No patient died of bleeding from the sutureless fixation site. Two deaths were due to renal causes: one, renal artery occlusion secondary to postoperative redissection, and one, nonocclusive renal failure. Two patients died of thrombosed grafts. There was one death each from gangrene of the bowel secondary to obstruction of the superior mesenteric artery by the original dissection, ruptured abdominal aortic aneurysm, sepsis, bowel ischemia, multisystem failure, bleeding from a previously unrecognized gastric carcinoma, stroke, and exsanguination from an unspecified source. The operative mortality in the different centers ranged from 0% to 50%. The importance of this wide spread must be interpreted in light of the fact that a large number of teams performed less than a handful of these operations. Duration of aortic

Table 2. Descending Thoracic Aortic Grafting With Sutureless Prosthesis

Disease	No. of Patients	Presentation	No. of Patients	Distal Perfusion	No. of Patients	Aortic Clamping Time (min)	No. of Patients	Graft Type	No. of Patients	Operative Mortality: Disease	No. of Patients	Deaths	%
Dissection		Hemothorax	3	LA-FA	3	1–10	14	Standard	64	Dissection			
Acute	24	Shock/arrest	6	FV-Ao	2	11–20	11	Modified	11	Acute	24	8	18.6
Chronic	19	Rupture	7	FV-FA	11	21–30	6	Elongated	5	Chronic	19		
Aneurysm		Expansion	4	Shunt	8	31–45	4	Unknown	1	Aneurysm			
As	29	Uncomplicated	9	None	56	48 ± 14	11			As	29	3	10.3
Mycotic	2	Unknown	52	Unknown	1	24 (14–34)	3[a]			Mycotic	2	1	50.0
Trauma	7					16 (6–45)	8[a]			Trauma	7	0	0
						Unknown	24						
Total	81		81		81		81		81		81	12	14.8

[a] Data are shown as the mean with the range in parentheses.

As = atherosclerotic; FV-FA = femoral vein–femoral artery; FV-Ao = femoral vein–aorta; LA-FA = left atrium–femoral artery.

cross-clamp time appeared to influence operative mortality.

All 7 patients with traumatic transection of the descending thoracic aorta in the collective experience were men. Thus, most of them probably had larger aortas, and smaller grafts must have been rarely used. Partial cardiopulmonary bypass from femoral vein to descending aorta was used in one operation and the "clamp and connect" technique in four operations. No information about the method of protection of the distal circulation was available for the two other procedures. Aortic cross-clamp times of 9, 21, 28, and 45 minutes were reported for 4 patients. The size of the implanted prosthesis was specified for only 2 patients. One of them received an 18-mm graft and exhibited prolonged hypertension postoperatively [7]. All 7 patients survived without paraplegia, renal failure, or reoperation for bleeding.

Follow-up Information

Follow-up information was reported for 143 of the 217 patients receiving an intraluminal device. The longest postoperative interval was 112 months. However, the data for the different disease processes and the various operative sites were not always separated, and therefore long-term outcome was analyzed for the entire population rather than for each subset of grafting.

Three late deaths, one from hemoptysis and two from redissection, may have been graft related. However, no late clinical manifestations of prosthetic dysfunction were reported.

At least 34 aortograms, four computed tomographic scans, and unspecified numbers of digital subtraction angiograms as well as magnetic resonance images were obtained at various but not clearly defined intervals postoperatively. These examinations showed normal configuration and position of the prosthesis without pseudoaneurysm formation, thrombosis, stenosis, or migration. An undisclosed number of randomly selected patients were tested for graft-related hemolysis and anemia up to 4 years postoperatively without abnormal findings. Postmortem examinations of a small cohort who died 3 to 51 months after the operation showed dense fibrous union between the aorta and the graft without pathology either at the fixation sites or within the body of the prosthesis.

In 1989 at the Annual Meeting of The Society for Vascular Surgery, Crawford [26] commented that he encountered "17 patients who had such grafts [sutureless] inserted elsewhere . . . [with] partial luminal obstruction, kinking of the graft, chronic hemolysis and anemia and persistence of aneurysm between graft and major aortic branch vessel, i.e., coronary arteries, innominate artery, subclavian artery, and celiac axis." In a personal communication, Crawford failed to provide further details but wrote: "I have concluded that this is a very unsatisfactory method and would prefer the standard end to end anastomosis by suture."

The nature of these complications suggests that the poor results were not due to flaws inherent in the sutureless concept but rather to faulty operative technique, such as implantation of excessively long grafts or failure to replace all diseased aortic tissue. Borst [27] noted in an Editorial Comment that "In our hands both placement of the ring and subsequent slippage have been a problem . . . Several cases of erosion of these rings of [sic] the aortic wall leading to formation of false aneurysms have been recorded." Kirklin and Barratt-Boyes [28] referred in their textbook to 2 patients with type A dissection in whom progressive aortic regurgitation developed after replacement of the ascending aorta with sutureless grafts. The authors attributed the complication to "transection of the inner layer of the dissection at the proximal ligature" and concluded that "this suggests that resuspension of the valve is less good with this technique."

Comment

The published experience provides an opportunity to examine 217 instances of replacement of the thoracic aorta with an intraluminal sutureless prosthesis. In the course of these operations, at least 364 sutureless connections were constructed between the prosthesis and the aorta. The method was employed for a wide variety of aortic disorders. Except for four operations, the Bard prosthesis was used and proved readily adaptable for a variety of thoracic aortic replacement operations. The more recently introduced Meadox device permits easier and better approximation of optimal graft length than the fixed-sized Bard model and obviates the need for the time-consuming intraoperative elongation maneuver. The limited published experience with the newer device, however, precludes a meaningful evaluation.

The present review does not permit definitive conclusions about the advantages of sutureless over conventional suture methods of grafting the thoracic aorta. Our general knowledge about this procedure is drawn from retrospective reports supplemented by personal experience. Randomized or even matched prospective studies are not available. The majority of reported series are small, and the results are highly variable. Accurate evaluation is further handicapped by the heterogeneous surgical populations, the lack of a uniform standard of reporting, and the incomplete information about crucial variables such as patient condition on presentation, aortic cross-clamp times, blood loss, and follow-up. In spite of the shortcomings, however, the published experience provides sufficient material about the main features of sutureless grafting to permit tentative conclusions.

Insertion of the sutureless graft has proved to be a relatively simple procedure. It can be accomplished expeditiously and has been associated with few and mostly preventable intraoperative mishaps. The anticipated fracture, pressure necrosis, or disruption of the aorta from fastening the fixation ligature did not materialize either in the acutely dissected and friable vessel or in the atherosclerotic and noncompliant vessel. The false lumen produced by the dissection was obliterated by the fixation ligature. From the 364 known instances of sutureless anastomoses, only a handful of spool dislodgments, obstructions or thromboses due to kinking, and spool-related fatal aortic tears have been reported. Most of the complications were probably due to technical errors and can be prevented through stricter adherence to the correct method of implantation.

Despite the great variation in aortic cross-clamp times at the different centers, it is apparent that grafting is faster with the sutureless than with the conventional suture technique.

Although quantitative information about blood loss associated with sutureless grafting is limited, the available blood balance data, the repeated qualitative comments, the low incidence of exsanguinating hemorrhage or reoperations for excessive bleeding, and our experience convey a distinct impression that bleeding is appreciably less and more easily controlled with sutureless than with sutured prostheses. The virtual absence of persistent or uncontrollable bleeding from the graft connection sites not only reduces blood transfusion requirements but also shortens the duration of mechanical circulatory support, aortic clamping, and indeed the length of the entire operation. A major source of complications associated with the suture technique is thereby neutralized.

The relatively low morbidity of sutureless grafting is especially impressive with operations on the descending thoracic aorta. The nearly routine use of the standard two-ring prosthesis, with the greatest timesaving potential, in this location probably accounts for the low incidence of ischemia-related complications, such as paraplegia and nonocclusive renal failure. Furthermore, the short insertion time encourages replacement of the descending thoracic aorta without the use of mechanical circulatory support and thereby eliminates the serious complications associated with these systems without enhancing the risk of spinal cord or renal injury.

The operative mortality rate for replacing the ascending and descending thoracic aorta with sutureless grafts was 13.1% and 14.8%, respectively. The experience with arch replacement was too small for meaningful comment. Considering the limited experience of a large number of reporting teams, these results appear superior to the figures published with the sutured anastomosis technique. A valid comparison between the two methods of grafting, however, is not possible without randomized or matched clinical trials and more complete reporting of the relevant data. Nonetheless, it is reasonable to assume that with its demonstrated advantages, sutureless grafting enhances the safety of the operation.

Long-term function of the sutureless graft is encouraging. Published follow-up data suggest that the securely fixed and correctly sized graft does not migrate, kink, thrombose, stenose, leak, or produce hemolysis. In the limited autopsy material, the prosthesis was securely incorporated by the host aortic wall. The observations by Crawford [26] about late complications probably relate to poor surgical technique rather than to flawed design of the prosthesis itself. The comments of Borst [10] about erosion of the aortic wall by the fixation spool are of greater concern, as they point to a possible flaw in the ligature fixation concept. Additional follow-up studies are necessary to determine the incidence of these undesirable sequelae. In the meantime, the information obtained from the collective experience suggests that the intraluminal sutureless graft reduces the operative risks associated with the conventionally sutured prosthesis and offers comparable long-term function. Thus, judicious use of the sutureless prosthesis for replacement of the thoracic aorta is justified. Unless the reservations expressed through the anecdotal accounts are confirmed and the problems are not correctable, the sutureless technique may well gain gradually increasing acceptance.

Addendum

Since submission of this article a report was published on sutureless grafting of the thoracic aorta in 36 cases of dissection and 3 cases of aneurysm [29]. The series included 19 ascending, 13 arch, 1 combined arch and ascending, and 5 descending aortic replacements. There were seven hospital deaths (18.4%). Follow-up of 34 patients from 1 day to 8 years revealed one redissection, near the proximal fixation of an ascending aortic graft, possibly related to the sutureless connection site. There were no other graft-related complications or clinically apparent hemolysis.

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Homograft Replacement of the Aortic Valve

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Practice Guidelines in Cardiothoracic Surgery

During the last 10 years, members of our specialty have been fielding, on an individual and on a collective basis, requests regarding standards of care as they relate to our patients. These requests have come mainly from third-party payors on a national level, as well as private carriers, and also from medicolegal committees within our specialty organizations. The Council of The Society of Thoracic Surgeons, after much deliberation involving many council meetings, ultimately decided that these requests were legitimate and that a carefully structured response from our specialty was indeed indicated. From the outset, it was decided that these documents should represent the opinions of our specialty as completely as possible and, therefore, the active participation and support of the other three major thoracic societies (the American Association for Thoracic Surgery, the Western Thoracic Surgical Association, and the Southern Thoracic Surgical Association) have been solicited.

The committee and subcommittees formed as a result of this action of the Council of The Society of Thoracic Surgeons have met on many occasions and have had considerable deliberations concerning these matters. First of all, a title for these documents was thoroughly discussed; the use of the word "guidelines" seemed most appropriate and perhaps "minimal guidelines" would be even more appropriate. There was a clear understanding among the participants that this was not to be an effort to provide a textbook description of each procedure with a detailed analysis of every facet of patient care and outcome analysis, but rather it was to be a simple description of those things that are normally anticipated in developing the indications for surgery, as well as simple statements regarding those things to be anticipated before, during, and after the operative procedure in the care of the patient. It also was agreed that an attempt would be made to provide some broad-range outcome statements. It was also understood that, even though this work product could be entitled "minimal guidelines," some of the items identified might not be included in the care of an individual patient. Further, it was clearly understood that many other items might logically and appropriately be included in patient care and not included in these minimal guidelines.

Finally, and perhaps most importantly, it was agreed upon that this work product should be a "living document" and that frequent review and revision would be a part of the work intended. With the rapid advance of technology and patient care techniques, this final point is essential. Because of the volume of this effort, it will not be published in total form, but rather in the various elements of our specialty as the work product is completed and publication is appropriate. Because of the nature of the presentation of this material to thoracic and cardiovascular surgeons, it is clearly understood that revision of the first published portions of these documents may well be indicated prior to completion of the coverage of our specialty. Because of this, comments and suggestions regarding these guidelines are encouraged and solicited and should be addressed to the management of The Society of Thoracic Surgeons. It is our commitment to act upon these comments and suggestions and to revise and maintain this living document in a timely fashion.

George G. Lindesmith, MD
President, The Society of Thoracic Surgeons
1988–1989

Background

During his tenure as President of The Society of Thoracic Surgeons, George G. Lindesmith appointed the Ad Hoc Committee for Cardiothoracic Surgical Practice Guidelines. The current committee composition is as follows:

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ROBERT M. VANECKO, Chicago
ANDREW S. WECHSLER, Richmond

The organizational meeting of the Committee was held in Boston, Massachusetts, on May 8, 1989. During this and subsequent meetings, the guideline format and its degree of complexity were discussed extensively. It was recognized that practice guidelines were being constructed by many organizations, each with its own agenda and requirements. Therefore, guidelines varied in detail and complexity according to the perceived needs of the constituency. Furthermore, it was noted that there are no universally accepted guidelines for writing practice guidelines. However, to help the STS committee formulate its plan, guidelines already in existence or being developed were collected from other medical and peer review organizations, third-party payors, and both federal and state governments. This information was invaluable in assisting the Committee in arriving at its decisions regarding the structure and complexity of cardiothoracic surgical practice guidelines. After careful and extensive deliberation, it was decided to approach Practice Guidelines under the following rubrics:

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1. **The guidelines would be procedure-oriented.** Appropriate CPT codes were to be indicated. This would allow appropriate identification of each procedure as it would be coded in the revised CPT-4 code book. The Society's CPT-4 Advisory Committee, under the Chairmanship of Sidney Levitsky, was assisting in the revision of the cardiothoracic surgical codes which in many instances were out of date or in which codes were entirely lacking for procedures such as thoracic organ transplantation and left ventricular assist device insertion. Furthermore, listing of the procedure and diagnostic codes would assist members in their practice and other bodies in identifying the exact procedure being performed.
2. **The field of cardiothoracic surgery would be divided anatomically and associated pathologic processes in each area would be addressed.** Although the guidelines were to be procedure oriented, the field of cardiothoracic surgery was organized along anatomic and pathologic lines. Organization of the guidelines in this manner was decided upon to allow ease of categorization and implementation. This apparent ambivalence was accepted to facilitate guideline development, yet encompass the entire field of cardiothoracic surgery. Although some organizations that developed practice guidelines had struggled with this apparent dichotomy between disease entities and procedures, the Committee felt its approach was practical and would expedite this complex process.
3. **The criteria published by the American College of Obstetricians and Gynecologists* would be used as the model for the outline of the areas to be addressed for each Practice Guideline.** Their outline is:

   Procedure
   Indication
   Confirmation of Indication
   Action Prior to Procedure
   Contraindications

   Additions were made to this outline to address aspects not included in that outline and to make it more compatible with our needs. The subsequent headings decided upon by the Committee were:

   Diagnosis
   Procedure
   Indication
   Confirmation of Indication
   Relative Contraindications
   Actions Prior to Procedure
   Actions During Procedure
   Actions Following Procedure
   Outcome
   References

It was decided that cardiothoracic surgical textbooks would be the references of choice. There were many reasons for this decision, not the least of which was that these would represent the generally accepted view in the cardiothoracic surgical community, and only a few references would be required, thereby avoiding extensive and cumbersome bibliographies. For newer procedures for which textbook references were incomplete or unavailable, it was agreed that appropriate references from the cardiothoracic surgical literature would be supplied.

In view of the increasing emphasis by many upon outcome, it was agreed to include some estimate of expected outcome for each procedure.

Subcommittees for each cardiothoracic surgical category were appointed with a member of the Ad Hoc Committee as chairman of the subcommittee. These subcommittees and their membership are as follows:

1. Ischemic Heart Disease

   ROBERT H. JONES, CHAIRMAN
   GERALD M. LAWRIE
   WEI-I LI
   BRUCE W. LYTLE

2. Valvular Heart Disease

   THOMAS D. BARTLEY, CHAIRMAN
   JOSEPH M. CRAVER
   ROBERT A. GUYTON

3. Thoracic Aortic Disease

   JOSEPH S. COSELLI, CHAIRMAN
   E. STANLEY CRAWFORD
   RANDALL B. GRIEPP
   NICHOLAS T. KOUCHOUKOS
   D. CRAIG MILLER

4. Chest Wall, Diaphragm, Mediastinum, Pericardium

   THOMAS B. FERGUSON, CHAIRMAN
   LARRY R. KAISER
   KEITH S. NAUNHEIM
   CHARLES L. ROPER
   WILLIAM F. SASSER

5. Esophageal Disease

   ROBERT M. VANECKO, CHAIRMAN
   ROBERT J. GINSBERG
   ALEX G. LITTLE
   MARK B. ORRINGER

6. Bronchopulmonary Disease

   RICHARD G. FOSBURG, CHAIRMAN
   JOHN R. BENFIELD
   RICHARD M. PETERS
   THOMAS W. SHIELDS

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* Quality Assurance in Obstetrics and Gynecology, 1988 Edition, The American College of Obstetricians and Gynecologists, 409 12th St SW, Washington, DC 20024-2188.

7. Transplantation (heart, lung, heart-lung) and Heart Assist Devices

D. GLENN PENNINGTON, CHAIRMAN
WILLIAM A. BAUMGARTNER
A. MICHAEL BORKON
JACK J. CURTIS
VERDI J. DiSESA
J. KENT TRINKLE

8. Electrical Problems (pacemakers, arrhythmias, AICD)

MARVIN POMERANTZ, CO-CHAIRMAN
W. GERALD RAINER, CO-CHAIRMAN

9. Congenital Heart Disease

GEORGE G. LINDESMITH, CHAIRMAN
JEFFREY M. DUNN
HILLEL LAKS
WINFIELD J. WELLS

James A. DeWeese, MD, serves as liaison between the cardiothoracic surgical organizations and the vascular surgical organizations, the North American Chapter of the International Cardiovascular Society, and the Society for Vascular Surgery. These vascular surgical organizations are developing practice guidelines for vascular surgery. This method of cooperation has been adopted to avoid reduplication of effort.

Each subcommittee was charged with the development of guidelines for that category of cardiothoracic surgical practice. In rare instances a procedure might be potentially addressed by more than one subcommittee. Any possibility for overlap was resolved by the parent committee. As an initial effort, each subcommittee was requested to develop guidelines for three of the most commonly performed procedures in its area of expertise. These practice guidelines were then reviewed and critiqued by the entire Ad Hoc Committee and all subcommittees. After refinement, the final results were submitted to the Council of The Society of Thoracic Surgeons for approval. It was anticipated that this complex ratification process might develop snags. Therefore initially, the introductory, preoperative evaluation, and institutional requirement sections along with guidelines for nine procedures were submitted for approval. It was anticipated that any potential problems with this review process that arose could then be resolved making ratification of future guidelines easier. Because in any extensive and complex review process as outlined there might be some differences of opinion, it was proposed that the Council of The Society of Thoracic Surgeons would be the final arbiter. The goal of this review process is to achieve consensus, but at the same time recognize that practice guideline development is, and always will be, a dynamic process.

It was decided that the first iteration of the guidelines be published every few months in *The Annals of Thoracic Surgery*. On the following pages are the first set of practice guidelines and the introductory, preoperative evaluation, and institution requirement sections. It is anticipated that eventually guidelines covering the entire specialty will be collated and published as a separate document. It should be emphasized that one of the most important aspects of this process is that these guidelines will require continual modification and revision as clinical cardiothoracic surgical practice changes.

I would like to thank the members of the Ad Hoc Committee and of each subcommittee for their effort and excellent cooperation.

George C. Kaiser, MD
Chairman, Ad Hoc Committee for Cardiothoracic Surgical Practice Guidelines

Introduction

The following sections provide basic practice guidelines for those individuals qualified in the specialty of cardiothoracic surgery. Although the practice of medicine requires a strong scientific foundation, medicine is also an art requiring both intuitive skills and good judgment. Occasionally, objective decisions concerning patient management must be modified depending upon such factors as individual patient characteristics or other associated factors. Such cognitive functions are an integral and essential part of the practice of cardiothoracic surgery with regard to preoperative patient evaluation, selection of operative procedures, and postoperative patient care until the patient has recovered. The ability to modify the process as needed for the greater benefit of the patient is vital if an optimal outcome is to be achieved for each patient. These intuitive and cognitive skills are essential to the successful practice of cardiothoracic surgery and must be applied in every phase, frequently requiring modification of the patient's care from preoperative preparation to discharge planning. These intellectual abilities are developed, sharpened, and maintained by constant exposure to patients in a clinical setting. In addition, the practitioner must update his or her fund of scientific information by journal review, attendance at scientific meetings and postgraduate seminars, as well as by consultation with colleagues both inside and outside of the specialty of cardiothoracic surgery.

Because guidelines are but one aspect in the ever-evolving field of cardiothoracic surgery, it is anticipated that these guidelines must be modified frequently to keep pace with the advances. As a background upon which practice guidelines will be developed, it is pertinent to delineate the extent of expertise encompassed by the specialty of cardiothoracic surgery. This has already been done.

> Scope of Thoracic Surgery[†]
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> The thorax or chest extends from the neck to the abdomen and contains the principal organs of the circulatory and respiratory and upper gastrointestinal systems. The specialty of thoracic surgery consists of the diagnosis and

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[†] Modified from "Guidelines for Hospital Privileges for Thoracic Surgeons," developed by The Society of Thoracic Surgeons, endorsed by The American Association for Thoracic Surgery in 1986, and revised in 1991 and 1992. Copies may be obtained from: The American Association for Thoracic Surgery, Thirteen Elm St, Manchester, MA 01944; or The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611-4267.

treatment of the major organs comprising the thorax, but is not totally confined to this area. More precisely, it includes the surgical treatment of congenital anomalies, malfunctions, diseases, and injuries of the thoracic cage, the heart and great vessels, the tracheobronchial system and lungs, esophagus, diaphragm, other mediastinal contents, and circulatory systems in all age groups.

This specialty is recognized by certification by the American Board of Thoracic Surgery or fellowship in cardiovascular and thoracic surgery in the Royal College of Surgeons of Canada, or certification of special competence in general thoracic surgery by the Royal College of Surgeons of Canada. Certification requires specific training in an approved residency program which educates its students in both the diagnosis and treatment of diseases, malfunctions, and injuries of the thoracic cavity and its contents. This requires a detailed knowledge of normal and abnormal anatomy and physiology within the cardiorespiratory and gastrointestinal systems. Specific technical and cognitive skills must be learned both in the operating theater and in the post surgical setting which allow for excision, repair or replacement (via tissue transplant or prosthesis) of the contents of the thorax. These abilities must include detailed knowledge of and expertise with the operative techniques, the medications, and technological hardware required for the safe and expeditious performance of these procedures.

Fields of expertise practiced by thoracic surgeons include: 1) Benign and malignant tumors of the lung, chest wall, esophagus and stomach and mediastinal contents; 2) Coronary artery disease and its complications; 3) Diseases of the great vessels; 4) Valvular heart disease; 5) Electrophysiological arrhythmia ablation and pacemakers; 6) hernias and other pathology of the diaphragm; 7) Malfunctions of the esophagus; 8) Congenital and developmental anomalies of the cardiovascular system, diaphragm, esophagus, trachea and all structures within the chest; 9) Gastrointestinal endoscopy; 10) Bronchoscopy, thoracoscopy, and mediastinoscopy; 11) Peripheral vascular surgery as associated with major vessel disease; and 12) Blunt and sharp injuries to the thorax (trauma) including preoperative diagnosis, surgical evaluation, operative management and postoperative care.

An appropriately trained and credentialed thoracic surgeon should be expected to request privileges in those areas covered by his training. Training in Canadian programs is not in every case equivalent to that required by the ABTS. In those instances, the actual training received must be evaluated in the process of granting privileges. Those privileges may include, but not be limited to, the following list:

Thoracic and cardiovascular surgical privileges (for adults and children)

All operations involving resection, reconstruction, repair or biopsy of the lung and its parts (e.g. pneumonectomy, lobectomy, segmentectomy, localized resection, sleeve resection, in continuity with chest wall resection, including transplantation, etc., but not limited to these); and procedures incidental to the above.

All operations involving resection of the chest wall or the pleura, such as resection of chest wall tumor, pleurectomy, decortication, thoracoplasty, resection of first (or other) rib(s), empyema drainage, sternoplasty (for pectus excavatum or carinatum), etc., but not limited to these; and procedures incidental thereto.

All operations involving resection, reconstruction or repair of the trachea and bronchi, such as tracheostomy, tracheal resection, bronchotomy, bronchoplasty, etc., but not limited to these; and procedures incidental thereto.

All operations involving resection, reconstruction or repair of the esophagus and diaphragm, such as diverticulectomy, esophagectomy, esophagogastrectomy, colon interposition, jejunal interposition, hiatal herniorrhaphy, removal of diaphragmatic tumors, repair of the diaphragm, etc., but not limited to these; and procedures incidental thereto.

All operations of the pericardium, involving resection, reconstruction, drainage, etc., such as pericardiectomy or pericardiotomy, but not limited to these; and procedures incidental thereto.

All endoscopic procedures and instrumentations involving the esophagus and tracheobronchial tree, such as laryngoscopy, bronchoscopy, thoracoscopy, esophagoscopy, esophageal dilatation, etc., but not limited to these; and procedures incidental thereto.

Lymph node and superficial biopsy procedures, such as scalene or axillary node biopsy, subcutaneous and muscular biopsy etc., and procedures incidental thereto.

All procedures involving biopsy, excision of tumor, drainage, etc., of the mediastinum, such as mediastinoscopy or mediastinotomy, but not limited to these; and procedures incidental thereto.

Closed heart operations, both congenital and acquired (including reconstruction with grafts)

Open heart operations, both congenital and acquired (including valvuloplasty, replacement, reconstruction with grafts or transplantation)

Surgery of tumors of the heart and pericardium

Surgery of arrhythmias (arrhythmias ablation)

Surgery for implantation of artificial heart and mechanical devices to support or replace the heart partially or totally.

Correction or repair of all anomalies or injuries of great vessels and branches thereof, including aorta, pulmonary artery, pulmonary veins, venae cavae, but not limited to these; and procedures incidental thereto.

All operations for myocardial revascularization (endarterectomy, bypass grafts or internal mammary artery or other grafts to coronary arteries).

Operative procedures for correction or palliation of arteriosclerotic vessels, including the aorto-iliac-femoral system, but not limited to these; and procedures incidental thereto.

All operations for placement or replacement of cardiac pacemaker systems, including multi-chamber sensory pacemakers, automatic implantable defibrillators, whether epicardial or pervenous approach, but not limited to these; and procedures incidental thereto.

All operations involving transplantation of the heart, heart-lung block, and single or double lung transplants.

These guidelines have been developed by the Ad Hoc Committee for Cardiothoracic Surgical Practice Guidelines of The Society of Thoracic Surgeons. Numerous professional organizations have been involved in the development of the practice guidelines, and there is a diversity of opinion concerning their format and content. Because there are no established standards for writing practice guidelines, they have tended to vary from organization to

organization according to the perceived needs of the particular specialty.

The Society of Thoracic Surgeons has elected to develop guidelines that are brief, broadly interpretable, helpful to practicing clinical cardiothoracic surgeons, and useful to those assessing quality of cardiothoracic surgical care. After considerable deliberation and discussion, the guideline format developed by the American College of Obstetricians and Gynecologists[‡] was modified to fulfill the needs of practicing cardiothoracic surgeons and their patients. The guidelines were then developed and modified during an arduous review process. The general outline includes the following: Diagnosis, Procedure, Indication, Confirmation of Indication, Relative Contraindications, Actions Prior to Procedure, Actions During Procedure, Actions Following Procedure, Outcome and References. To make these guidelines relevant to cardiothoracic surgical practice, coding diagnoses with their codes and the procedure codes are indicated in each guideline. Lack of appropriate codes for newer procedures made coding difficult, if not impossible, in some instances.

From the inception of this task, it was acknowledged that practice guidelines could not and should not be all-inclusive. The development and application of guidelines must remain a dynamic process. Principles considered essential or important in a guideline at one time might become irrelevant or inappropriate at a later time. Extensively detailed and documented guidelines for the entire field of cardiothoracic surgery would approach the size of a textbook of cardiothoracic surgery, and would be obsolete before they were published.

Cardiothoracic surgical textbooks are updated frequently. Many of the Committee members have been contributors to these texts. Their selection as textbook contributors and Committee members acknowledges their clinical expertise in the field of cardiothoracic surgery. These guidelines have been developed by subcommittees of selected experts and educators, knowledgeable in the field of cardiothoracic surgery and especially the specific area to which they were assigned. Their curricula vitae will be available for review at the business office of The Society of Thoracic Surgeons.

As an initial entry into the field of practice guideline development, subcommittees in each of nine areas of the field of cardiothoracic surgery were charged with developing guidelines for three of the more commonly performed procedures in their designated area. These areas are: ischemic heart disease; valvular heart disease; thoracic aortic disease; transplantation and assist devices; arrythmias; bronchopulmonary disease; chest wall, diaphragmatic, mediastinal, and pericardial disorders; congenital heart disease, and esophageal disease.

After thorough deliberation, it was decided to have these guidelines procedure oriented. The thrust for development of these guidelines was to assure the opportunity for the best and most complete cardiothoracic surgical care for each patient. Issues of appropriateness and quality must be defined before cost can be assessed. The Committee is aware of its responsibility to each patient and to society to deliver this care in the most cost-efficient manner.

General recommendations that are applicable to the delivery of care to all cardiothoracic patients are presented separately. Basic preoperative evaluation and the necessary supporting services are identified in the following sections.

The Preoperative Evaluation

To be certain that the contemplated operation will not propose an undue risk to the patients, those who are candidates for a major thoracic or cardiac procedure should undergo a thorough preoperative evaluation. This evaluation is designed to detect concomitant medical diseases that might prove to contraindicate operation or that may require further treatment in preparation for the proposed surgical procedure. The following represents the minimum required preoperative evaluation and should be performed within one week of the date of operation.

1. Thorough history and physical examination
2. Chest roentgenogram
3. Urinalysis
4. Electrocardiogram
5. Blood sample for typing in all patients and a type and crossmatch for blood products in cases having a risk of significant blood loss. Patients who have previously provided blood via autologous donation may be excused from this requirement.
6. Blood analysis to include complete blood count, platelet count, PT, PTT and SMA-18.
7. Room air blood gas determination including pCO_2, pO_2, and pH in patients with suspected pulmonary compromise.
8. Appropriate medical consultation where indicated.
9. Assessment of nutritional status.

Institutional Requirements

There are certain institutional requirements that must be met if cardiothoracic surgery is to be safely performed within a health care center. These include:

1. Blood Bank—The performance of cardiac surgery necessitates an active and competently managed blood bank. At times, a blood bank may be called upon to provide large quantities of many different types of blood components with little or no notice. The presence of such a facility within the hospital is mandatory if major cardiothoracic surgery is to be performed safely.
2. Intensive Care Units—Adequate postoperative care often mandates complex equipment for treatment and the monitoring of many hemodynamic indices and

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[‡] Quality Assurance in Obstetrics and Gynecology, 1988 Edition, The American College of Obstetricians and Gynecologists, 409 12th St SW, Washington, DC 20024-2188.

other clinical parameters simultaneously. A hospital should have both the equipment for and medical, nursing, and ancillary personnel experienced in postsurgical critical care delivery if patient needs are to be met satisfactorily. Due to the needs for emergency intervention which occasionally arise in the postoperative period, there should be a physician on call within the hospital, preferably one with experience in the care of critically ill patients.

3. Anesthesiology—The safe performance of cardiothoracic surgical procedures requires a cooperative effort between surgeon and anesthesiologist. The critical nature of these patients and the multiple cardiopulmonary manipulations that inevitably occur require anesthesiologists who are expert in the delivery of care to patients with complex cardiac and thoracic problems. These anesthesiologists must be familiar with all types of ventilators, monitoring equipment, and other supportive equipment. Anesthesiologists with special interest in cardiothoracic surgical problems are preferable.
4. Operating Rooms—Both postoperative complications and primary cardiothoracic emergencies frequently require urgent operative intervention. An institution must therefore have the capability to rapidly mobilize surgical and support teams for emergency procedures 24 hours a day, seven days a week.
5. Medical Consultation Services—Supportive expertise must be available 24 hours a day, seven days a week in medical subspecialty fields such as cardiology, pulmonology, neurology, hematology, nephrology, and infectious disease.
6. Respiratory Therapy—The modern delivery of critical care requires around the clock availability of respiratory care personnel familiar with the operation, function, and maintenance of a wide variety of modern life support equipment.
7. Radiology—Around the clock radiologic services must be available in the fields of diagnostic radiology and nuclear medicine.
8. Laboratory and Pathology Services—Around the clock laboratory services must be available for immediate blood gas analysis and determination of serum biochemical and hematologic including coagulation values.

EDITOR'S NOTE:

This is the second set of guidelines to be published. The first set, on three procedures in the areas of chest wall, diaphragm, mediastinum, and pericardium, appeared in the April issue of *The Annals of Thoracic Surgery* (Ann Thorac Surg 1992;53:729–37).

Practice Guidelines

Ischemic Heart Disease: I

Diagnosis:	410	Acute myocardial infarction
	410.8	Acute myocardial infarction of septum alone
	429.71	Acquired cardiac septal defect
Procedure:	33545	Repair of postinfarction ventricular septal defect
Indication:	Demonstration of left-to-right shunting at the ventricular level in a patient after myocardial infarction	
Confirmation of Indication:	1)	Oxygen step-up on right heart catheter
	2)	Indicator-dilution curve or cardiac imaging shunt study showing left-to-right shunt at the ventricular level
	3)	Echocardiography
	4)	Cardiac catheterization sometimes appropriate
Relative Contraindications:	Risk judged greater than benefit	
Actions Prior to Procedure:	1)	Confirm presence of VSD
	2)	Coronary arteriography sometimes appropriate
Actions During Procedure:	Repeat shunt study to document closure	
Actions Following Procedure:	1)	Cardiorespiratory support
	2)	Treat arrhythmias
Outcome:	1)	Mortality of 10% to 60% determined by preoperative status
	2)	Discharge 7 to 21 days determined by preoperative status and postoperative complications
	3)	Elimination or diminution of left-to-right shunt

References

1. Hill JD, Stiles QR. Acute ischemic ventricular septal defect. Circulation 1989;79(Suppl 1):112-5.
2. Kirklin JW, Barratt-Boyes BG. Postinfarction ventricular septal defect. In: Kirklin JW, Barratt-Boyes BG, eds. Cardiac surgery. New York: Wiley, 1986:301-10.

Practice Guidelines

Ischemic Heart Disease: II

Diagnosis:

414.0	Coronary atherosclerosis
414.9	Chronic ischemic heart disease, unspecified

Procedure: Coronary artery bypass grafting (autologous vein or arterial graft)

33510	1-V CABG
33511	2-V CABG
33512	3-V CABG
33513	4-V CABG
33514	5-V CABG
33516	6+-V CABG

Indication:

1) Stable angina pectoris
2) Unstable angina pectoris
3) Angina equivalent syndromes
4) Acute myocardial infarction
5) Exercise-induced congestive heart failure
6) Acute coronary occlusion or dissection after catheterization or angioplasty
7) Ischemic cardiomyopathy prior to other major surgical procedures
8) Resting ischemic electrocardiographic change
9) Positive exercise treadmill test
10) Radionuclide perfusion defect
11) Exercise ejection fraction less than 0.50
12) Ischemic ventricular arrhythmias
13) Left main stenosis of 50% or greater vessel diameter
14) Stenosis of three major coronary arteries
15) Stenosis of two major coronary arteries, including proximal LAD stenosis
16) Stenosis of 50% or greater in any coronary vessel in a patient undergoing cardiac operation for another cause (valve replacement, left ventricular aneurysm resection, electrophysiologic procedure, post-myocardial infarction VSD)
17) Atherosclerotic vein graft to coronary vessels
18) Failure of previously placed conduit
19) Coronary artery aneurysm
20) Intraoperative coronary occlusion or embolization
21) Acute aortic dissection involving or occluding coronary ostia
22) Ventricular septal defect or cardiac rupture
23) Left ventricular aneurysm with angina
24) Refractory ventricular tachycardia or congestive heart failure

	25)	Ischemia-induced mitral regurgitation
	26)	Ventricular tachycardia or ventricular fibrillation not associated with left ventricular aneurysm
Confirmation of Indication:		Coronary arteriography and/or noninvasive testing as indicated
Relative Contraindications:		Risk judged greater than benefit
Actions Prior to Procedure:		Examine for potential conduit to be used for bypass
Actions During Procedure:	1)	Confirm suitability of conduit
	2)	Confirm adequate size and quality of arterial sites for graft insertion
Actions Following Procedure:	1)	Cardiorespiratory support
	2)	Treat arrhythmias
Outcome:	1)	1% to 20% mortality determined by patient age and condition, associated disease, coronary anatomy, and left ventricular function
	2)	Discharge in less than ten days in uncomplicated cases
	3)	Relief of ischemic symptoms

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1. Spencer FC. Bypass grafting for coronary artery disease. In: Sabiston DC Jr, Spencer FC, eds. Surgery of the chest. Philadelphia: W.B. Saunders, 1990:1820–38.
2. Kirklin JW. Guidelines and indications for coronary artery bypass graft surgery. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Coronary Artery Bypass Graft Surgery). J Am Coll Cardiol 1991;17:543–89.

Practice Guidelines

Ischemic Heart Disease: III

Diagnosis:	414.10	Left ventricular aneurysm
Procedure:	33542	Resection or plication of left ventricular aneurysm
Indication:	1)	Congestive heart failure
	2)	Systemic emboli
	3)	Angina pectoris
	4)	Ventricular arrhythmias
Confirmation of Indication:	Cardiac imaging study with contrast, echocardiography, or radionuclide technique showing dyskinesia	
Relative Contraindications:	Asymptomatic true aneurysm	
Actions Prior to Procedure:	1)	Coronary arteriography
	2)	Left ventriculography often indicated
Actions During Procedure:	1)	Remove mural thrombus
	2)	In presence of ventricular tachycardia, map endocardium and ablate sites of early repolarization
Actions Following Procedure:	1)	Cardiorespiratory support
	2)	Treat arrhythmias
Outcome:	1)	Mortality of 3% to 30% determined by patient age, general status, associated disease, and extent of myocardium involved
	2)	Discharge in 7 to 21 days depending on preoperative status
	3)	Diminution or relief of symptoms

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1. Harken AH. Left ventricular aneurysm. In: Sabiston DC Jr, Spencer FC, eds. Surgery of the chest. Philadelphia: W.B. Saunders, 1990:1766–76.
2. Magovern GJ, Sakert T, Simpson K, et al. Surgical therapy for left ventricular aneurysm. A ten-year experience. Circulation 1989;79(Suppl 1):102–7.

CORRESPONDENCE

Response of Internal Mammary Artery to Sympathomimetic Agents

To the Editor:

I read with interest the recent letter by van Son and associates [1] on pharmacological response of internal mammary artery (IMA) and gastroepiploic artery. In their letter, they emphasized the differences between IMA and gastroepiploic artery in pharmacological responses to vasoactive agents. They have found that up to approximately 3 to 4 cm proximal to the epigastric bifurcation, the IMA is completely elastic, whereas its first 5 cm as well as the last section is elastomuscular. From these observations, von Son and associates hypothesized that the vasospasm of the IMA may be significantly more apparent in the elastomuscular sections of the IMA and its continuation into the muscular superior epigastric artery and musculophrenic artery. I agree with their opinion because it is in accord with our clinical and experimental findings [2, 3].

Van Son and associates quoted our report on the functional study of β-adrenoceptor function in the IMA [2] and stated "A study by He and colleagues confirms our hypothesis of a limited reactivity of the IMA to sympathomimetic drugs." I wish to advise that there may be some misunderstanding on this topic. In our study, we found that β-adrenoceptor agonists only induced a weak relaxation in the human IMA, ie, the β-adrenoceptor function is weak in this artery. However, this should not be misunderstood as if the IMA responded to sympathomimetic drugs poorly. Sympathomimetic agents include α-adrenoceptor agonists (phenylephrine, methoxamine), β-adrenoceptor agonists (isoproterenol), and α- plus β-agonists (epinephrine, norepinephrine). In large arteries, α-adrenoceptors mediate contraction whereas β-adrenoceptor mediate relaxation [4]. Our findings on β-adrenoceptors in the IMA suggest that in this artery functional β-adrenoceptors are sparse. This does not imply that the α-adrenoceptors are sparse as well. In contrast, we have focused on studies of the contraction in the IMA [2, 3, 5] and we found that the human IMA contracted strongly to the thromboxane A_2 mimetic U46619 and α-adrenoceptor agonists (phenylephrine and norepinephrine) [3]. We suggested that these constrictors may be possible spasmogens for the IMA. Others have obtained similar results [6]. In addition, our further study on α-adrenoceptors in the IMA will be published soon. Therefore, one cannot conclude that the reactivity of the IMA to sympathomimetic drugs is limited. I believe that the distal portion of the human IMA (at the level below the fifth rib and proximal to the bifurcation where the segments of the IMA studied in our experiments were taken from) is pharmacologically active to vasoactive agents and is a place where spasm could occur in response to thromboxane A_2 or sympathomimetic agents (α-adrenoceptor agonists).

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1. Van Son JAM, Smedts F. Pharmacological response of internal mammary artery and gastroepiploic artery. Ann Thorac Surg 1991;51:864.
2. He G-W, Buxton B, Rosenfeldt F, Wilson AC, Angus JA. Weak β-adrenoceptor-mediated relaxation in the human internal mammary artery. J Thorac Cardiovasc Surg 1989;97:259–66.
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5. He G-W, Angus JA, Rosenfeldt FL. Reactivity of the canine isolated internal mammary artery, saphenous vein, and coronary artery to constrictor and dilator substances: relevance to coronary bypass graft surgery. J Cardiovasc Pharmacol 1988; 12:12–22.
6. Weinstein JS, Grossman W, Weintraub RM, Thurer RL, Johnson RG, Morgan KG. Differences in α-adrenergic responsiveness between human internal mammary arteries and saphenous veins. Circulation 1989;79:1264–70.

Atrial Fibrillation and Flutter After Open Heart Operation

To the Editor:

We read with interest the article by Fanning and associates [1] concerning prophylaxis of supraventricular tachyarrhythmias with magnesium sulfate after coronary artery bypass grafting.

In this letter we present our experience with atrial fibrillation and flutter, with special regard to predictors and to prophylactic postoperative digitalization. An outline of treatment is also briefly provided.

A total of 1,530 consecutive patients undergoing cardiac operation and treated postoperatively with digitalis to prevent supraventricular tachyarrhythmias were observed to evaluate the onset of sustained atrial fibrillation and flutter. They were 1,082 male (average age, 56.9 years) and 448 female patients (average age, 52.6 years). Patients with previous supraventricular arrhythmias, high-degree atrioventricular block, proved sensitivity to digoxin, and renal failure (creatinine clearance < 70 mL/min) were excluded from the study. Administration of amiodarone, β-blockers and digitalis, if done, was suspended 7, 2, and 1 days respectively, before operation. Sixty-four percent (979 patients) underwent myocardial revascularization; 23.1% (353 patients), valvular operation; 7.7% (118 patients), radical correction of congenital cardiopathies; and 5.2% (80 patients), various associated procedures. All patients were given 0.4 mg of digitalis (Cedilanid; Sandoz, Milan, Italy) intravenously within 2 hours postoperatively, and the dose was repeated after 12 hours. An additional 0.4 mg was given in two separate doses intravenously on the first and second postoperative days, and 0.25 mg was given by mouth each day for the next 7 days.

All patients underwent continuous electrocardiographic monitoring for 48 hours; standard 12-lead electrocardiograms were obtained daily for 3 days postoperatively and on the day before recovery. After transfer from the intensive care unit and suspension of continuous monitoring, cardiograms and rhythm stripes were obtained whenever the pulse became irregular or was recorded to be outside the range of 50 to 130 beats/min. We also performed an extensive analysis of 24 variables: 8 preoperative (age, sex, hypertension, diabetes, smoking, left atrial dilatation, ejection fraction, drugs); 4 intraoperative (aortic cross-clamp time, cardioplegia, incomplete coronary revascularization, ventricular defibrillation); and 12 postoperative (shock, myocardial infarction, stroke, central venous pressure, inspired oxygen fraction, potassium level, free triiodothyronine level, free thyrox-

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ine level, anemia, infection, drugs, mediastinal drainage). For reversion to sinus rhythm amiodarone or verapamil was used indifferently.

The mean overall incidence of sustained atrial fibrillation and flutter was 12.1% (ranging from 5.9% in congenital correction to 21.7% in associated procedures); the incidence was only 7.8% in myocardial revascularization. Incidence of arrhythmias was greater within the first 48 postoperative hours (54.1% of patients) and in patients aged 60 years and over (58.3% of patients). Reversion to sinus rhythm was obtained with amiodarone in 144 patients (previous treatment with verapamil was ineffective in 29 patients), with verapamil in 22 patients, and with late direct-current conversion in 17 patients (3 were receiving amiodarone and 17 were receiving verapamil). In 2 patients arrhythmias persisted at the time of recovery. There was no greater incidence of cardiovascular morbidity or mortality suggesting digitalis toxicity.

Atrial fibrillation and flutter are relatively frequent after cardiac operations, ranging from 8% to 100% [2, 3], and age has been suggested as the most important predictor [4, 5]. If we consider only sustained atrial fibrillation and flutter occurring after coronary bypass grafting, their incidence ranges from 11.4% to 40% [6]. Discordance exists as to whether digitalization is effective [2] to reduce the incidence of such arrhythmias or not [6]; similarly, many therapeutic regimens aimed at preventing arrhythmias and at establishing and maintaining sinus rhythm have been tested [1, 3].

In conclusion our data suggest age only, and none of the other 23 risk factors considered, as predictive of atrial fibrillation and flutter after open heart operations. Patients undergoing associated procedures are at higher risk for development of such arrhythmias, whereas the incidence is only 7.8% in patients undergoing myocardial revascularization. Immediate postoperative digitalization, according to the guidelines proposed, is risk-free, well-tolerated, and effective in prophylaxis of sustained major supraventricular tachyarrhythmias, limiting to only 12.1% the mean overall incidence of atrial fibrillation and flutter. Reversion to sinus rhythm is obtained with both amiodarone and verapamil, even if the first one seems to be more effective.

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Reply

To the Editor:

We thank Drs Santoli, Di Mattia and Scrofani for their interest in our report. Their letter supports previously published data suggesting that atrial fibrillation after cardiac operations is more common in the elderly [1]. Given the observational nature of their report it does not justify the conclusion that postoperative digitalization is effective prophylaxis for supraventricular tachyarrhythmias (SVT) after cardiac operations.

The incidence of SVT after cardiac operations seems to vary with the sophistication of the techniques used for their detection. White and associates [2] studied 41 patients undergoing coronary bypass and found by using a 7-day continuous Holter tape recording system that some SVT developed in all patients in the postoperative period, although many episodes were clinically insignificant.

Although relatively frequent, postoperative SVT do not seem to adversely affect the perioperative mortality or long-term survival of patients undergoing coronary artery bypass [3]. As such, strategies to prevent the occurrence of SVT in the postoperative period should be relatively benign. Some controlled clinical trials support the use of β-blockers (usually propranolol) or digitalis in preventing SVT, whereas other studies refute such claims [4]. Verapamil has also been effective in preventing SVT, but with a high incidence of unacceptable side effects [5]. These conflicting results are related in part to the relatively small size of most studies, variations in the methods of arrhythmia detection, lack of a standardized definition of a "clinically significant" arrhythmia, and most importantly our fundamental ignorance of the pathogenesis of postoperative SVT.

Further work on this common problem should be directed not only at prevention but, more importantly, at defining the causes of postoperative SVT. Recent considerations include the disruptive mechanical effects of right atrial cannulation [6], inadequate right atrial myocardial protection [7], diminished myocardial magnesium content [8], and altered atrial β-receptor density [4].

A more complete understanding of the pathogenesis of postoperative SVT should facilitate the use of specific perioperative prophylactic measures and thereby replace the current empiric approaches to this problem.

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Cardioplegia With Fluorescein for Visualization of Coronary Arteries

To the Editor:

The article "Intraoperative coronary angiography using fluorescein" [1] has three bibliographic references, and none of them describe the use of fluorescein in coronary arteries. This may give the false impression that this procedure was originally designed by the authors. However, 10 years ago my colleagues and I published [2] an experimental work on dogs using a similar technique, pointing at the same aims. This experimental work could be done in an operating room and was well documented on a photograph.

I wish a good future for the techniques, and I hope the omission in the bibliography will be corrected in future publications.

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Reply

To the Editor:

I appreciate the opportunity of responding to the comments of Dr Burstin concerning our recent article [1]. Coronary angiography using fluorescein had been already performed 10 years ago. Experimentally visualizing the coronary artery and the area of blood supply to myocardium using fluorescein is a well-known method. There are several experimental reports using this method, including the interesting article of Burstin and associates [2–6]. The purpose of our clinical article is to demonstrate the usefulness of this method for evaluating the efficacy of revascularization intraoperatively. In this sense, we cited the references that reported various other methods used for the same purpose. We were acquainted with the interesting article by Burstin and associates, but for this reason we did not cite it in the references.

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Total Cavopulmonary Connection

To the Editor:

Pearl and associates [1], in reviewing the historical development of the total cavopulmonary connection, state: "Exclusion of all but the lateral wall of the right atrium from the venous to pulmonary connection was first introduced by Puga and colleagues in 1987" [2]. However, the concept of the total cavopulmonary connection was first introduced 7 years earlier, in 1980, as the major part of a one-stage repair of hypoplastic left heart syndrome [3].

As the procedure has become successfully and widely used, it was of interest and satisfaction to read Anderson's assessment [4] of this 1980 report and of our fundamental contribution to the development of total cavopulmonary connection.

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Retrograde Coronary Sinus Cardioplegia Using the Magic Bubble: Simplified Steps to Avoid Problems

To the Editor:

Retrograde coronary sinus cardioplegia (RCSC) has been shown to be effective, safe, and equivalent to myocardial protection with standard antegrade techniques. Due to the simplicity of the system and homogeneous distribution of cardioplegia solution, RCSC has become my method of choice for all aortic valve operations, complex aortic procedures, mitral valve operations, and complex coronary artery operations including reoperations. Because of the increased use of RCSC, a simplified approach using single right atrial cannulation and a "magic bubble" as a marker for correct coronary sinus cannulation has evolved and been used without problems in the last 100 patients.

The technique is as follows. The patient is placed on cardiopulmonary bypass using a double-stage single venous cannula through the right atrial appendage. The aorta is cross-clamped and warm blood antegrade cardioplegic arrest is instituted (unless severe aortic insufficiency is present). The RCSC catheter is placed through an incision 1 to 2 cm inferior to the base of the atrial appendage, keeping the catheter anterior to the venous cannula with a slight J-bend at the tip. The RCSC catheter is aimed at the anterolateral aspect of the tricuspid valve, rotating clockwise around the annulus until the coronary sinus ostium is entered. External digital palpation must verify that the RCSC catheter is below the level of the inferior vena cava in the atrioventricular groove. The balloon is then inflated, the catheter secured, and its position rechecked. While antegrade cardioplegia is administered, dark venous blood should rise in the RCSC catheter if balloon occlusion is correct.

When cold retrograde blood cardioplegia is begun, a small bolus of air ("magic bubble") is left in the catheter. The acute angle of the heart is lifted slightly to expose the posterior descending vein, and with initiation of the RCSC, a bubble of air can be seen traveling along the posterior system, ensuring the catheter position is correct. Retrograde coronary sinus cardioplegia is administered at pressures not to exceed 40 mm Hg while right and left ventricular temperatures are monitored; muscle temperatures are kept less than 20°C.

Before the removal of the aortic cross-clamp, warm retrograde blood cardioplegia is instilled to raise the myocardial temperature above 30°C, after which the aorta is released and the RCSC catheter removed.

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Medtronic-Hall Valve

To the Editor:

A number of questions have arisen regarding our group's experience with the Medtronic-Hall valve prosthesis, which was published in *The Annals of Thoracic Surgery* [1]. Clearly the Medtronic-Hall valve is one that we have used for many years and with much confidence, and is a valve whose mechanical durability and hemodynamic function is highly dependable. Our group, however, has switched to the exclusive use of the St. Jude Medical bileaflet prosthesis. The reasons for relying on the St. Jude valve as our mechanical valve of choice at the University of Pittsburgh are its ease of handling, durability, low thromboembolic complication rate, and the exceedingly low incidence of tissue or suture impingement, which is seen occasionally with the Medtronic-Hall valve. One other element that has influenced our decision to switch to the St. Jude valve is our active role in resident training and the relative ease of using the St. Jude valve in a resident teaching setting. We hope this letter serves to clarify our position on our mechanical valve of choice and our present practice.

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Reference

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Plateletpheresis and the Cost of Heart Operations

To the Editor:

We recently published the results of a study in which the harvesting of platelets and leukocytes before cardiopulmonary bypass significantly decreased postoperative bleeding and improved postoperative pulmonary function by attenuating the microembolic and inflammatory consequences of platelet activation [1]. We now have information from the accounts department of our institution that shows a dramatic decrease in the average cost of coronary artery bypass grafting in those patients having had high-yield platelet harvesting.

An uncomplicated perioperative course is the key to profitability in major heart operations. Major complications translate directly to increased costs through added procedures and increased length of stay. Extra time spent in a weakened condition in an intensive care unit is extremely expensive. The Medicare patient population contains the elderly and higher risk patients, and therefore improvements in morbidity would be expected have the maximum impact on charges generated by this group.

Ideally the introduction of new technology should improve patient care and reduce its cost. In the absence of cost-benefit analyses, the introduction and acceptance of new technology can be retarded.

Our hospital accounts department studied the financial impact

Table 1. Coronary Artery Bypass Grafting With and Without Plateletpheresis

Group	Number	Length of Stay	Charges Generated
Without PLP	102	14.7 ± 10.6	$38,746 ± 29,296
With PLP	92	13.2 ± 6.4	$31,996 ± 9,174
Difference (p value)		1.5 (p = 0.12)	$6,750 ($p$ = 0.018)

PLP = plateletpheresis.

of the introduction of this procedure. They provided information on 102 Medicare patients undergoing coronary artery bypass grafting between July 1990 and March 1991 and compared it with information on 92 consecutive Medicare patients undergoing coronary artery bypass grafting after the introduction of routine high-yield plateletpheresis. These data are summarized in Table 1 and demonstrate significant cost reductions achieved when coronary artery bypass grafting is accompanied by plateletpheresis. Data were analyzed by independent *t* test and are presented as mean ± standard deviation.

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Surgical Repair of Coarctation of the Aorta in Infants and Children

Having read the articles on surgical treatment of coarctation of the aorta as presented at the symposium "Current Controversies and Techniques in Congenital Heart Surgery" (Baltimore, MD, Sep 8–9, 1989) [1–3], we are still left with controversy regarding the optimal management of this common congenital anomaly. Because our group was involved in the recent exchanges in *The Journal of Thoracic and Cardiovascular Surgery* concerning this topic [4–9], we would like to comment on various aspects of surgical management of coarctation of the aorta as presented in the aforementioned articles.

First of all, we fully agree with Dr Moulton's note that, to avoid late aneurysm formation, patch angioplasty should be avoided for primary repair of coarctation, even in the case of a long tubular stenosis or an anomalous right subclavian artery, for which Messmer and associates [1] advocate this technique. In patients with an additional symptomatic anomalous right subclavian artery, we recommend reimplantation of this vessel in the ascending aorta, either through a right thoracotomy at a later stage or through a median sternotomy in the case of simultaneous coarctation repair [10]. Patch angioplasty may still be indicated in certain patients with restenosis at the coarctation repair site.

We believe that Messmer and associates' and Jonas' articles [1, 2] quite eloquently review the advantages and disadvantages of the various surgical techniques. We have abandoned use of the subclavian flap angioplasty (SFA) in favor of resection and end-to-end anastomosis because of similar reasons as outlined by Jonas, namely: (1) There is an unequivocal lack of evidence of superior hemodynamics distal to the coarctation repair site after SFA (versus resection and end-to-end anastomosis) in infancy [5]. (2) There is histological evidence that after SFA, especially at neonatal age, residual ductal tissue may lead to restenosis at the coarctation repair site [11, 12]. The potential of ductal tissue to induce coarctation is also evident from a study by Rao and associates [13] in which the restenosis rate after balloon angioplasty was significantly higher when performed in infancy than thereafter. (3) Subclavian flap angioplasty requires sacrifice of the left subclavian artery. In a recent study we have reported that the capacity of physiological augmentation of blood flow in the left arm may be severely compromised after SFA, even when performed in infancy [14]. This, in our view, major disadvantage of the SFA technique, which may potentially lead to serious functional impairment of the left upper extremity, has not been adequately emphasized in any of the aforementioned articles. (4) Subclavian flap angioplasty does not lend itself to augmentation of the hypoplastic distal aortic arch. (5) There is a potential risk of late aneurysm formation in the posterior aortic wall after resection of the ductal tissue in SFA.

The findings of Siewers and co-workers [3] that the hypoplastic transverse aortic arch in infants in whom coarctation was resected subsequently showed accelerated growth is interesting and important because a less radical reconstruction of the transverse arch may potentially reduce the operative risk. An important question, however, is whether and to what degree leaving the hypoplastic aortic arch unrepaired in these usually severely sick patients, who frequently have associated complex intracardiac anomalies, will adversely influence the postoperative survival, because any strain imposed on the left ventricle may further compromise its function. The combined early and late mortality in the groups of Siewers and associates [3] and Lacour-Gayet and co-workers [4] of 45% and 23%, respectively, attest to the fact that early complete relief of the obstruction produced by the coarctation and the hypoplastic transverse aortic arch (if possible, together with repair of associated complex intracardiac anomalies, as performed by Lacour-Gayet and associates) may be beneficial for the recovery of the strained left ventricle. In addition, complete relief of the obstruction produced by the coarctation and the hypoplastic arch may also reduce the risk of recoarctation [8]. Thus, in summary, although the indications for techniques designed to enlarge the hypoplastic transverse aortic arch in addition to resection of the coarctation and the isthmus and creation of a maximally wide anastomotic diameter of the inferior aspect of the aortic arch should in general probably be less stringent [15, 16], such techniques are perhaps still indicated in infants with compromised left ventricular function due to coarctation, severe hypoplasia of the transverse aortic arch, and additional complex intracardiac anomalies.

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Twenty-eighth Annual Meeting
The Society of Thoracic Surgeons

The Twenty-eighth Annual Meeting of The Society of Thoracic Surgeons was held at the Walt Disney World Dolphin Hotel in Lake Buena Vista (Orlando), Florida, on February 3–5, 1992, with an attendance of 3,238 registrants, including spouses and exhibitors. The Scientific Sessions were attended by 835 members, 66 Candidate members, and 480 guests, including 161 residents, for a total of 1,381 physician attendees.

There were 858 registrants present at the Twenty-fifth Annual Postgraduate Course. At the Postgraduate luncheon, David J. Cohen spoke on "Military Preparations for Managing Thoracic and Cardiovascular Trauma in International Conflicts." Co-Chairmen Cary W. Akins and Robert J. Ginsberg and the members of the Committee on Postgraduate Education are to be commended for putting together an excellent program, which produced the highest Postgraduate attendance in the history of The Society.

Breakfast Sessions were held on two mornings. Attendance at each was limited to ensure informality and encourage member participation. The first Breakfast Session was devoted to case presentations of difficult problems and the second to small clinical workshops on selected topics. The J. Maxwell Chamberlain Memorial Paper was presented by Marshall L. Jacobs and was co-authored by William I. Norwood, Jr, and John D. Murphy. New this year were the well received "How I Do It" technical sessions. The success of these sessions and the scientific program was due chiefly to the substantial effort of the Program Committee under the vigorous leadership of Delos M. Cosgrove III and Douglas J. Mathisen.

Robert W. Jamplis' Presidential Address was entitled "If Not the Art, Why the Science?" It appears in this issue of *The Annals*. The Herbert Sloan lecture on "The International Cardio-thoracic Surgeon" was presented by Mark V. Braimbridge of the Rayne Institute, St. Thomas Hospital in London, England. Mr Braimbridge was elected an Honorary Member of The Society.

Meredith L. Scott and Robert B. Trumbo co-chaired the Local Arrangements Committee. Mrs Meredith Scott (Susan) chaired the Spouses' Hospitality Committee. The Annual Reception took place at the Disney-MGM Studios Theme Park. Drs Scott and Trumbo did an excellent job of planning for the various activities in connection with the meeting.

The Eighth Spouses Postgraduate Program was organized by Mrs Harold C. Urschel, Jr (Betsey). A good turn-out of spouses attended this Postgraduate course, entitled "Energy Engineering and Creative Problem Solving: You Don't Have to End the Day Exhausted," presented by Ann McGee-Cooper.

At the Annual Business Meeting, the following officers were elected: Vincent L. Gott, *President*; Denton A. Cooley, *Vice President*; Richard P. Anderson, *Secretary*; Nicholas T. Kouchoukos, *Treasurer*; and W. Gerald Rainer, *Historian*. James L. Cox, H. Storm Floten, and Timothy J. Gardner were elected *Councillors at Large*. Thomas B. Ferguson remains as *Editor* of *The Annals of Thoracic Surgery*. A complete list of the officers, committee members, and society representatives follows this report. The Society extends its appreciation to retiring officers and committee members for their dedicated service.

One hundred forty-nine new members were elected. The total membership now stands at 3,244.

The Smith, Bucklin staff are to be commended for their hard work and diligence, which produced an outstanding meeting.

The Twenty-ninth Annual Meeting will be held January 25–27, 1993, in San Antonio, Texas.

Richard P. Anderson, MD
Secretary

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6) Do not use your word processor's hyphenation capabilities. Do not right justify text. Use two hyphens for long dashes.

7) In tables, use only tabs, not spaces, to align columns.

II. *Organization and Delivery of Electronic Files*

1) Accepted manuscripts may be submitted on 3.5" or 5.25" diskettes, which must be either MS-DOS or Macintosh format. The author should retain copies of all files as backup. All diskettes must be accompanied by the *final* revision and a duplicate copy of the manuscript (including two clearly separated and labeled sets of illustrations) in full conformity with the standard Information for Authors on the preceding pages.

2) Diskettes should each be labeled with:
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3) If possible, it is helpful to have additional material such as tables, figure legends, and references saved as individual files—one file for each category. A file key should accompany the diskette.

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Collective Review

- **Rupture of the Airways From Blunt Trauma: Treatment of Complex Injuries**
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EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

■ Surgery of the Airways, Boston, Massachusetts—July 20–21, 1992

For information on this meeting, contact Thoracic Surgical Unit, Massachusetts General Hospital, Boston, MA 02114; or telephone (617) 726-2806 (facsimile: (617) 726-7667).

■ Contemporary Techniques for Aortic Valve Surgery: Homograft, Autograft, and Stentless Valve Implantation, Sardinia, Italy—August 24–29, 1992

For information on this meeting, contact Margo Irr, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

■ Course in Pulmonary Diagnosis, Bethesda, Maryland—September 1–4, 1992

The course will be presented by the Armed Forces Institute of Pathology and the American Registry of Pathology, Washington, DC, at the Hyatt Regency Hotel, Bethesda, Maryland. Course information may be obtained from Center for Advanced Medical Education, Armed Forces Institute of Pathology, Washington, DC 20306-6000; telephone: (301) 427-5231, FAX: (301) 427-5001.

■ Sixth Annual Meeting of the European Society for Vascular Surgery, Athens, Greece—September 2–4, 1992

For information on this meeting, contact ESVS '92 Congress Bureau, Euro Conference Center, B. Tower of Athens, Apt 604, 2-4 Mesogion St, Gr. 11527 Athens, Greece; or telephone 30(1)7787539 or 30(1)7717797 (facsimile: 30(1)7774584).

■ Forty-first International Congress of the European Society for Cardiovascular Surgery, Montpellier, France—September 6–9, 1992

For information on this meeting, contact ESCVS Congress 92, Le Corum, BP 2200-F 34027, Montpellier Cedex 1, France; or telephone (33) 67.61.67.61 (facsimile: (33) 67.61.67.00).

■ Sixth Annual Meeting of The European Association for Cardio-Thoracic Surgery, Geneva, Switzerland—September 14–16, 1992

For information on this meeting, contact Symporg S.A., 108, route de-Frontenex, CH-1208 Geneva, Switzerland; or telephone 41-22 786 37 44 (facsimile: 41-22 786 40 80).

■ Third International Live Teleconference on Homograft and Autograft Implantation, Harefield, England—October 8–10, 1992

For information on this meeting, contact Margo Irr, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

■ First International Meeting of Thoracic Surgery, Barcelona, Spain—October 9–10, 1992

For information on this meeting, contact Congress Secretariat, RCT asociados, Aulèstia i Pijoan, 12, 08012 Barcelona, Spain; or telephone 34-3-4156938 (facsimile: 34-3-4156904).

■ American College of Surgeons, New Orleans, Louisiana—October 11–16, 1992

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050 (facsimile: (312) 440-7014).

■ Concepts in Myocardial Revascularisation, Leicester, United Kingdom—October 15–16, 1992

For information on this international symposium, contact Mrs Fiona Legate, Department of Cardiology, Glenfield General Hospital, Groby Rd, Leicester, UK; or telephone (44) 533-871471, ext 3038 (facsimile: (44) 533-875792).

■ Myocardial Preservation: Past Trends and Future Technology, Atlanta, Georgia—October 16–17, 1992

For information on this meeting, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

■ Fifty-eighth Annual Scientific Assembly, American College of Chest Physicians, Chicago, Illinois—October 25–29, 1992

For information on this meeting, contact American College of Chest Physicians, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ Thirty-ninth Annual Meeting of the Southern Thoracic Surgical Association, Wesley Chapel (near Tampa), Florida—November 5–7, 1992

For information on this meeting, contact Southern Thoracic Surgical Association, 401 N Michigan Ave, Chicago, IL 60611-4267; or telephone (312) 644-6610 (facsimile: (312) 321-6869).

■ Cardiac Surgery 1993: State of the Art, St. Thomas, US Virgin Islands—November 12–14, 1992

The fifth annual conference for cardiac surgeons, perfusionists, nurses, and allied health personnel is sponsored by the Academy of Medicine of New Jersey and Cooper Hospital/University Medical Center, UMDNJ-Robert Wood Johnson Medical School at Camden. For further information, contact Rosemary Morrone: (609) 963-3757.

■ Sixty-fifth Scientific Session of the American Heart Association, New Orleans, Louisiana—November 16–19, 1992

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 373-6300 (facsimile: (214) 373-3406).

■ Le Club Mitrale—Live Teleconference, Paris, France—December 7–9, 1992

For information on this meeting, contact Lisa Turnbull, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

■ Twenty-ninth Annual Meeting of The Society of Thoracic Surgeons, San Antonio, Texas—January 25–27, 1993

For information on this meeting, contact Richard P. Anderson, MD, The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611; or telephone (312) 644-6610.

■ Third World Congress of the International Society of Cardio-Thoracic Surgeons, Salzburg, Austria—January 25–27, 1993

For information on this meeting, contact Prof Dr Felix Unger, c/o Interconvention, Austria Center Vienna, A-1450 Vienna, Austria; or telephone +43/1/23 69-26 43 (facsimile: +43/1/23 69-648).

■ Forty-second Annual Meeting of the American College of Cardiology, Anaheim, California—March 14–18, 1993

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone (800) 253-4636.

■ One Hundred Thirteenth Annual Meeting of the American Surgical Association, Baltimore, Maryland—April 1–3, 1993

For information on this meeting, contact American Surgical Association, Department of Surgery, CB 7245, University of North Carolina, 136 Burnett-Womack Building, Chapel Hill, NC 27599; or telephone (919) 966-4320 (facsimile: (919) 966-6009).

■ Seventy-third Annual Meeting of the American Association for Thoracic Surgery, Chicago, Illinois—April 26–28, 1993

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ World Congress on Diseases of the Chest, Amsterdam, the Netherlands—June 13–18, 1993

For information on this meeting, contact XVII World Congress on Diseases of the Chest, International Academy of Chest Physicians & Surgeons, 3300 Dundee Rd, Northbrook, IL 60062-2348.

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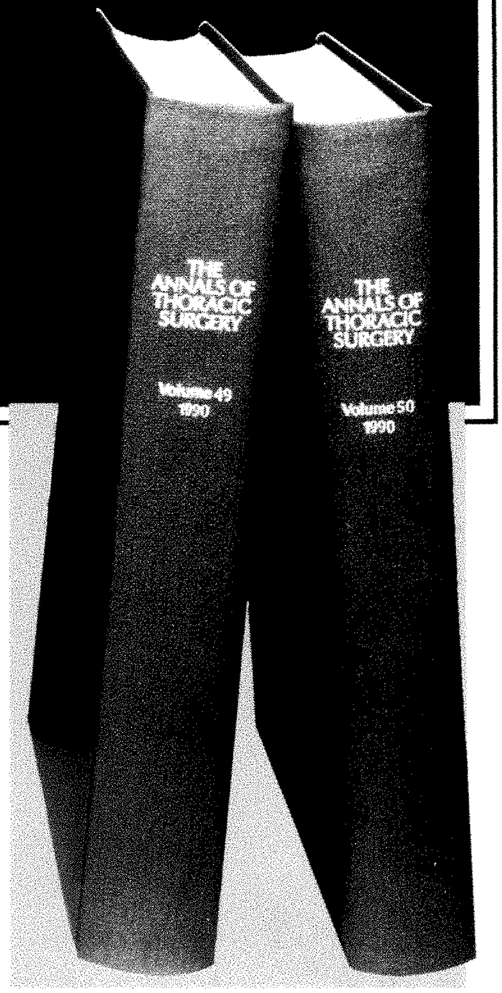
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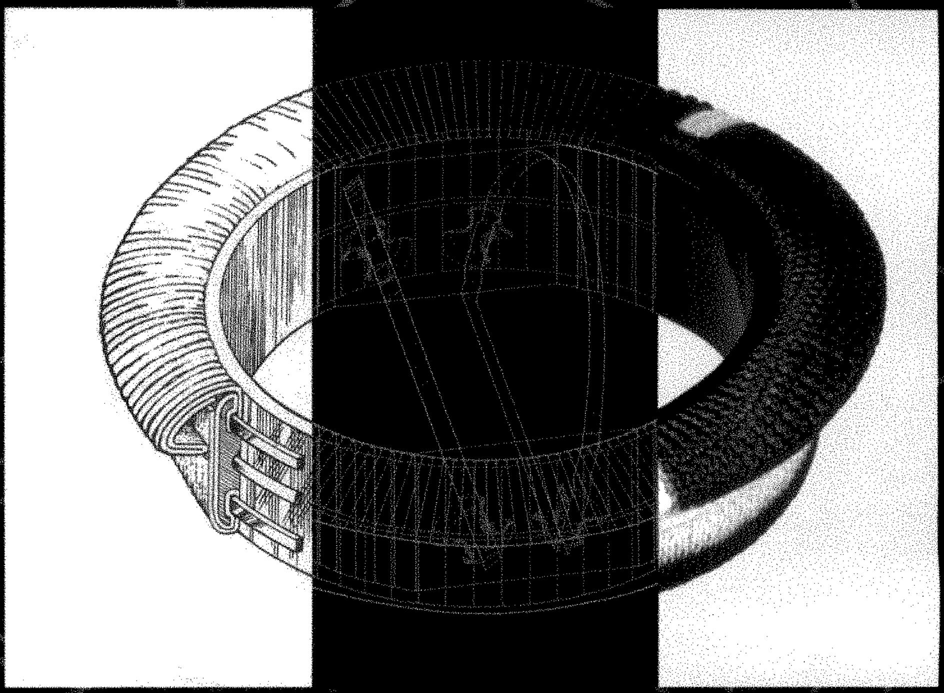

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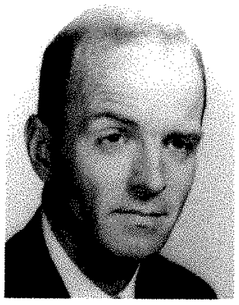
ANNOUNCEMENT

Editorial Board Changes

Two members are retiring from the Editorial Board this year. Robert W. Anderson and John M. Moran have completed nine-year terms. The Editor and The Society of Thoracic Surgeons are deeply grateful to these men for their scientific excellence, their dedication, and their many hours of hard work on behalf of *The Annals of Thoracic Surgery*. They were recognized at the Business Meeting at the Annual Meeting and were given certificates of appreciation.

Robert W. Anderson



John M. Moran

The Annals is pleased to announce the addition of three new members to the Editorial Board:

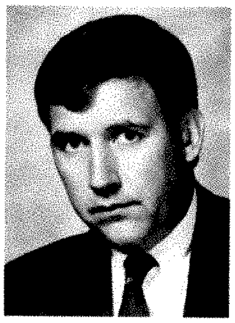
James E. Lowe, Professor of Surgery and Pathology, Director of Electrophysiology Service, Duke Medical Center, Durham, NC

Douglas J. Mathisen, Associate Professor of Surgery, Associate Visiting Surgeon, and Associate Chief, General Thoracic Surgery, Massachusetts General Hospital, Boston, MA

Larry W. Stephenson, Professor and Chief, Cardiothoracic Surgery, Wayne State University and Harper Hospital, Detroit, MI

James E. Lowe

Douglas J. Mathisen



Larry W. Stephenson

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R Adams Cowley, MD: 1917–1991

Herbert Sloan, MD

Section of Thoracic Surgery, University of Michigan Hospital, Ann Arbor, Michigan

On October 27, 1991, R Adams Cowley died of heart failure at his Baltimore home. He was 74. R (no period) was born of Mormon parents in Layton, Utah. He attended the University of Utah and graduated from the University of Maryland School of Medicine in 1944. After two years of training in general surgery at Maryland, he served in the Army of the United States in Europe and returned to the University of Maryland to complete his residency in general surgery in 1949. There followed two years of training in thoracic surgery at the University of Michigan. He then began his professional career at the University of Maryland, where in time he became Professor and Head of the Division of Thoracic and Cardiovascular Surgery at the University of Maryland. Also, he was Founder and Director of the Maryland Institute for Emergency Medical Services Systems. Dr Cowley is survived by his wife, Roberta, a daughter, Kay Pace, and a son, R Adams Cowley II, who was three weeks old at the time of Dr Cowley's death. Dr Cowley was buried with full military honors in Arlington National Cemetery.

The crowning achievement of Dr Cowley's professional life was the Maryland Institute for Emergency Medical Services Systems. He began with a vision of "the Golden Hour," the time during which prompt resuscitation and treatment of trauma patients will save most of them. This he translated into a transportation and treatment network in Maryland that was the first of its kind and finest in the world. The intense struggle to accomplish this covered three decades. He was variously characterized as dedicated, persistent, single-minded, politically astute, sometimes abrasive, and a remarkable organizer. He also had a healthy ego. A sign in an office at the Cowley Shock Trauma Center read:

> Yea, though I walk through the valley of the shadow of death I will fear no evil: for I'm the meanest son of a bitch in the valley.

It was just these characteristics that made R's contribution to the founding of The Society of Thoracic Surgeons so important. In a letter written in 1972 (R Adams Cowley, personal communication, Baltimore, 1972) to Dr Ellison, our historian, R said

> The more I thought about it, the more important it became for me that a new society should be created . . .
>
> Beginning in 1958 at every national meeting . . . I spoke to my elder colleagues . . . (but) there was either no support or the support was lukewarm.

In 1961 in Philadelphia, R met with several others to discuss this possibility. There were subsequent meetings in 1962 and 1963. By this time interest in a new society had increased markedly.

At a meeting of the John Alexander Society in April 1962, a group of "young Turks" led by R and Frank Byron urged that a society, limited to thoracic surgeons, be formed. It was decided that a committee, chaired by Dr Cowley, be appointed to explore the possibility of developing such a society. At the next meeting of the John Alexander Society in 1963, Dr Cowley reported on the recommendations of his committee. One of these was the formation of a new society of thoracic and cardiovascular surgeons. The rest is history! Dr Ellison described the origins and development of The Society in *The Annals of Thoracic Surgery* in 1972 [1] and 1984 [2]. In the latter paper, Dr Ellison presented in considerable detail the important part Dr Cowley played in the early history of The Society.

R was certainly a stormy petrel, and he reminded me of Norman Bethune. He confided to a close associate during particularly bitter fights how much he loved them (Stephen Turney, personal communication, Baltimore, 1992). It is altogether fitting that R Adams Cowley be recognized again for his important contributions to the origins of The Society of Thoracic Surgeons and that we pay tribute to a valiant, visionary warrior.

References

1. Ellison RG. Significant events in the history of The Society of Thoracic Surgeons. Ann Thorac Surg 1972;14:577–604.
2. Ellison RG. The Society of Thoracic Surgeons: the first twenty years. Ann Thorac Surg 1984;37:1–8.

Address reprint requests to Dr Sloan, Section of Thoracic Surgery, University of Michigan Hospital, 1500 E Medical Center Dr, 2120 TC, Ann Arbor, MI 48109-0344.

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Thoracic Surgeons and Clinical Trials: A Manifesto for the Future

Valerie W. Rusch, MD

Memorial Sloan-Kettering Cancer Center and Cornell University Medical College, New York, New York

The excellent editorial by Dr Richard Feins in the January 1992 issue of *The Annals* [1] brings to mind the old adage: "Today's conservatives worship yesterday's radicals." Otherwise stated, some individuals or institutions are only fully appreciated posthumously, especially when they have been ahead of their time. During the 12 years of its existence (1977 to 1989), the Lung Cancer Study Group (LCSG) pioneered prospective clinical trials in operable lung cancer and in other thoracic malignancies, but did not receive unqualified support from the thoracic surgical and oncologic communities for doing so. Increasingly, thoracic surgeons are recognizing that the LCSG, no matter what its weaknesses, laid vital groundwork in thoracic oncology and provided a unique vehicle for thoracic surgeons to participate in clinical trials. As Dr Feins points out, the demise of the LCSG has forced thoracic surgeons to disperse their clinical research efforts into multiple, larger cooperative groups. These efforts are based on the results of LCSG trials and on the traditions of meticulous staging, careful clinicopathologic correlation, and multidisciplinary care fostered by the LCSG. The legacy of the LCSG, and its influence on a new generation of thoracic surgeons, may be as important as the clinical trials it performed.

See also page 992.

For the past 4 years, there has been a half day meeting of thoracic surgeons involved in clinical trials in conjunction with the annual meeting of the General Thoracic Surgical Club. These meetings were initially for LCSG surgeons, but they are now a forum open to all surgeons interested in clinical trials. This year's meeting included reports from all of the major cooperative groups, from the M.D. Anderson and Memorial Sloan-Kettering Cancer Centers, and from the National Cancer Center of Japan. It is exciting to realize that more thoracic surgeons than ever are involved in clinical trials. They have taken a leadership role in developing 17 trials including 14 phase II or III lung cancer trials, one phase II trial and one phase III trial in esophageal cancer, and one phase III trial in malignant thymoma. Yet at this meeting there was a pervasive sense of frustration that thoracic surgeons have become a disenfranchised minority within the oncologic community. Since the demise of the LCSG, there has been no source of direct funding to thoracic surgeons involved in clinical trials. The development of surgically oriented trials in the cooperative groups is due to the altruistic goodwill and hard work of key thoracic surgeons. In contrast to the LCSG, the cooperative groups currently provide *no* data management support for surgeons. We have made do with data managers who work primarily for medical or radiation oncologists, and who therefore know little about surgical patients and surgical staging. No medical or radiation oncologist would agree to enter patients into cooperative group trials under similar circumstances, but surgeons are still widely regarded as noncognitive individuals who should be content to be passive conduits for patient accrual and the acquisition of tissue specimens.

However, an even more destructive situation became evident at the recent General Thoracic Surgical Club meeting. Several of the current lung cancer trials duplicate LCSG trials, using only slightly different chemotherapy. Worse yet, four of the phase III lung cancer trials *also partially or completely duplicate each other*. The two major cancer centers are either pursuing randomized trials that they cannot complete because of insufficient numbers of patients or performing phase II single-institution trials using a chemotherapy regimen unpopular in many institutions. Thus, many thoracic surgeons are involved in clinical trials, but their efforts are uncoordinated, duplicative, and counterproductive. Only two trials have managed to supersede this disarray by becoming intergroup trials: the current trial in operable esophageal cancer and the planned retinoid chemoprevention trial for resected T1 N0 non–small cell lung cancers. They are stellar examples of what *we can and should do.*

Sadly, some of the problems of duplication and fragmentation relate to the ego needs of physicians who desire to be principal investigators of a large clinical trial, and the wish of each of the cooperative groups to establish a presence in early stage lung cancer. Such ego needs are intolerable in view of the facts that the outcome of successful well-designed clinical trials in stages I through III non–small lung cancer will directly affect the care of 70,000 or more Americans, and that 400 patients or more are needed to achieve statistically meaningful results in many phase III trials. The number of patients willing to participate in clinical trials and the number of thoracic surgeons trained to perform those trials are relatively small. Therefore, we must combine our efforts and our patient populations if we are going to arrive at meaningful results in a timely manner.

How can this situation be remedied? Stated bluntly: we thoracic surgeons need to get our act together. In terms of sheer numbers, we will *always* be a minority by comparison with medical and radiation oncologists, but we do not

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Address reprint requests to Dr Rusch, Thoracic Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021.

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have to remain disenfranchised. For many reasons, the LCSG will not be reincarnated, so we must seek other solutions. Toward this end, I propose an 8-point program:

1. *Increase the frequency of our research meetings by making them semiannual.* With minimal, if any additional time expenditure or expense, we could also meet each fall in conjunction with the American College of Surgeons.
2. *Change the content of these meetings.* We should use these meetings to exchange information, to coordinate our efforts, and to decide which trials should be conducted in an intergroup manner.
3. *Seek expert advice.* Upon selected occasions, outside experts in oncology and tumor biology should be invited to these meetings to discuss future approachs to treatment and ways in which we can move promising laboratory findings into clinical trials. This "think tank" approach has worked very well for the National Surgical Adjuvant Breast Project, helping that group to develop trend-setting breast cancer trials. It could work well for us too.
4. *Spread the word.* At least one of the thoracic journals should consider publishing a brief report of each of these semiannual meetings, along with a list of current trials and their principal investigators.
5. *Develop uniform and fair policies for the authorship of manuscripts reporting intergroup trials.* Principal investigators from *each* of the participating cooperative groups and individuals who accrue the largest number of patients should be authors. There should be a policy for access to data so that subsidiary manuscripts analyzing particular aspects of a trial can be written, when appropriate. *All* of the "key players" must be given credit, and the mechanism for that credit must be established ahead of time.
6. *Demand higher standards of surgical involvement through peer review.* As a member of the Cancer Clinical Investigations Review Committee, the NCI peer review group that site visits all of the cooperative groups, I have placed before that committee a proposal that all clinical trials involving surgery be required to have a surgical principal investigator, a carefully written surgical treatment section, and surgical review of data forms. In addition, it has been proposed that there be a set of written standards for what constitutes state-of-the-art surgical staging and resection for each disease site. If peer review insists on high-quality surgical involvement, then the cooperative groups *will need to support our efforts to get refunded.*
7. *Demand our own funding for data managers and travel expenses to group meetings.* There are at least three mechanisms for such funding: (a) supplemental grant applications submitted in conjunction with the parent application for funding of a cooperative group, (b) requests for data managers specifically dedicated to surgeons, as part of an institutional grant application for participation within a cooperative group, and (c) if the previous two mechanisms fail—allocation of some of the group chairman's discretionary funds for surgical activities. The message to the cooperative groups must be loud and clear: if you want our patients and our expertise, you must fund our efforts.
8. *Educate ourselves and our residents.* To be fully enfranchised within the oncology community, we must speak the language. Ignorance of chemotherapy, radiotherapy, tumor biology, and clinical trials methodology is not acceptable. Expanding our fund of knowledge will make us better oncologists and will help us to develop better clinical trials. Most of us have acquired this knowledge indirectly over time because it was not formally provided in our training programs. Our residents should not have to do the same. The major thoracic societies should conduct annual or semiannual 1-day courses in thoracic oncology that cover the principles of surgical, medical, and radiation oncology. The content of such courses should include basic information about tumor biology, biostatistics, and clinical trials methodology.

The world of oncology is indeed dominated by nonsurgeons. This fact does not preclude our being leaders. Much of our fate as thoracic surgical oncologists resides in *our* hands. Let us set aside our individual agendas to work together. Let us not lose sight of our fundamental goals: to improve patient care, to foster resident education, and to reduce the high mortality of thoracic malignancies.

I am grateful to Drs John R. Benfield, Robert J. Ginsberg, and E. Carmack Holmes for their reviews of this editorial.

Reference

1. Feins RH. Thoracic surgery participation in cooperative group studies of cancer therapy. Ann Thorac Surg 1992;53:9–10.

EDITOR'S NOTE

For other editorials on lung cancer and clinical trials, see also:

1. Benfield JR. Adjuvant therapy of stage III non-small cell lung cancer. Ann Thorac Surg 1988;45:356.
2. Bunn PA Jr. Operation for stage IIIa small cell lung cancer? Ann Thorac Surg 1990;49:691.
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Effects of Temperature and Flow Rate on Regional Blood Flow and Metabolism During Cardiopulmonary Bypass

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Eleven dogs were subjected to a 150-minute period of cardiopulmonary bypass that consisted of a high-flow, normothermic phase, a high-flow, hypothermic phase, a low-flow, hypothermic phase, and then a high-flow, rewarming phase. Regional blood flow and oxygen consumption to the brain, intestines, kidney, and hind limb were determined at baseline and at 10-minute intervals during cardiopulmonary bypass. Blood flow to the carotid artery, superior mesenteric artery, and renal artery declined significantly with hypothermic cardiopulmonary bypass whereas blood flow to the femoral artery increased significantly. Although total body oxygen consumption returned to baseline values at the end of the rewarming phase, oxygen consumption for these regions differed somewhat from their baseline values. We conclude that blood flow during hypothermic cardiopulmonary bypass is shunted to skeletal muscle, particularly with high pump flows. Additionally, the return of total body oxygen consumption to baseline after rewarming is not necessarily reflected at the regional level.

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Cardiopulmonary bypass (CPB) is employed routinely and on a large scale. Its effects on the body have been studied extensively and many advances have been made, both in the CPB apparatus and in the methods by which it is performed. Nevertheless, it still is a cause of substantial postoperative morbidity and organ dysfunction.

Previous studies have looked at distribution of blood flow during CPB [1–9]. Likewise oxygen consumption for the whole body has been studied [10–12], as have isolated organ systems [13–15]. However, no studies have examined oxygen consumption for multiple organ systems. Furthermore, most studies have only examined 3 or 4 data points during the entire CPB period. This is one of the drawbacks of using microspheres for the measurement of organ blood flow. We undertook this study using ultrasonic arterial flow probes so that continuous blood flow measurements could be made, and a more dynamic picture of regional blood flow distribution and oxygen consumption could be observed.

Material and Methods

Study Design

Eleven conditioned, heartworm-free, female mongrel dogs (25 to 30 kg) were used to study regional blood flow, oxygen consumption, and lactate production during the different flow rates and temperatures normally employed for clinical CPB. Animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985). The CPB period consisted of 30 minutes of normal-flow normothermia (3.0 $L \cdot min^{-1} \cdot m^{-2}$, 38°C) followed by a 30-minute period of rapid cooling to achieve a rectal temperature of 25°C using a flow rate of 3.0 $L \cdot min^{-1} \cdot m^{-2}$. Then a 45-minute interval of low-flow, hypothermic CPB (1.5 $L \cdot min^{-1} \cdot m^{-2}$, 25°C) was employed followed by a 45-minute rewarming period (3.0 $L \cdot min^{-1} \cdot m^{-2}$, 38°C). Measurements of regional and total body oxygen consumption and lactate levels were performed at baseline before CPB and at 10-minute intervals during the different phases of CPB. Cardiac output and regional blood flows were measured at baseline; extracorporeal flow and regional blood flows were measured continuously during CPB.

General Preparation

After an overnight fast, with water permitted ad libitum, animals were premedicated with sodium pentobarbital (35 mg/kg intramuscularly), intubated and connected to a ventilator, and given inhalation anesthesia (isoflurane, 1.0% to 1.5%; 50% nitrous oxide). The body surface area was determined from a nomogram based on body weight [16]. A 20-gauge angiocatheter was placed in the left femoral artery for continuous blood pressure monitoring and arterial blood samples. A rectal temperature probe

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and urethral Foley catheter were inserted; electrocardiogram electrodes were placed for continuous electrocardiograph monitoring. A Swan-Ganz catheter was placed through the right external jugular vein and the tip was advanced into the pulmonary artery. The right common femoral artery and vein were exposed and a transit time ultrasonic flow probe (Transonics Systems Inc, Ithaca, NY) was placed around the femoral artery for continuous arterial flow measurements. A 20-gauge angiocatheter was placed in the femoral vein directed toward the foot for hind limb venous sampling. A 24-gauge plunge temperature probe was placed in the adductor muscle group of the right hind limb. The left common carotid artery and external jugular vein were likewise exposed and a flow probe was placed around the artery. The vein was cannulated with an 18-gauge angiocatheter in a cephalad direction so that the tip was at the base of the skull. A 24-gauge plunge temperature probe was placed in the forebrain through a small burr hole created with an 18-gauge needle through the frontal bone. At this point a baseline determination of central venous pressure, pulmonary artery systolic and diastolic pressures, and pulmonary capillary wedge pressure was made. The cardiac output using the thermodilution technique based on the Fick principle was measured and the systemic vascular resistance was calculated.

A midline laparotomy was performed and flow probes were placed around the superior mesenteric artery (SMA) and the right renal artery. A 19-gauge, 7-inch Silastic (Ethicon, Somerville, NJ) catheter was inserted into a midjejunal mesenteric venous tributary and advanced into the superior mesenteric vein. A balloon-tipped Swan-Ganz catheter was inserted into the left femoral vein and advanced into the right renal vein for renal vein sampling using the distal port on the catheter. Twenty-four–gauge plunge temperature probes were placed in the parenchyma of the right kidney and the wall of the midjejunum and secured with sutures. The abdomen was then closed, and after a 30-minute equilibration period the baseline measurements were repeated.

The chest was then entered through a midline sternotomy. The heart was exposed and suspended in a pericardial cradle. Heparin sulfate (400 U/kg) was administered intravenously to obtain an activated clotting time greater than 400 seconds. An 18F aortic cannula was inserted in a caudal direction into the right proximal common carotid artery for arterial perfusion. A 50F two-stage venous cannula was placed through a right atrial appendage incision and the tip was advanced into the inferior vena cava. After initiation of CPB, the ascending aorta was cross-clamped and the heart arrested with cold hyperkalemic crystalloid cardioplegia and enclosed in a cooling jacket kept at a temperature of approximately 10°C. The cardioplegia infusion was repeated at 20-minute intervals and as needed to keep the myocardial septal temperatures less than 15°C. During CPB, pancuronium bromide (0.1 mg/kg intravenously every 45 minutes) was given to prevent shivering.

The CPB apparatus consisted of a membrane oxygenator with a filtered hard-shell venous reservoir, using a nonpulsatile roller pump (Olson Medical Products Inc, Ashland, MA). In-line monitoring measuring extracorporeal blood flow, blood-gas analysis, and oxygen saturation was performed with the ultrasonic blood flow meter, Cardiomet 4000 extracorporeal blood gas monitoring system (Shiley, Inc, Irvine, CA), and OxySAT dual wavelength oximeter (Bentley Laboratories, Irvine, CA), respectively. Using an air-oxygen mixer (Cobe Laboratories, Lakewood, CO) arterial oxygen tension was maintained at greater than 200 mm Hg, and arterial pH was maintained between 7.40 and 7.45 during normothermia. During hypothermia, carbon dioxide was not added to the oxygenator, and the pH and carbon dioxide tension were allowed to rise and fall, respectively, according to the alpha-stat concept [17]. Perfusion pressure (Fig 1) varied between 60 and 80 mm Hg during normothermic, normal-flow CPB, between 55 and 60 mm Hg during hypothermic, normal-flow CPB, and between 40 and 50 mm Hg during hypothermic, low-flow CPB. Infusion of catecholamines was not used at any point during the experiment. Blood temperature was controlled with a cooler/heater (Cincinnati Sub-Zero, Cincinnati, OH). Cooling and heating of body temperature was also aided by use of a full-length water blanket placed under the animal and connected to a refrigerated/heated circulating water bath (VWR Scientific, Piscataway, NJ). The CPB circuit was primed with 1 L of Normosol-R solution (Abbott Laboratories, North Chicago, IL) and 500 mL of heterologous whole dog blood that had been obtained within 5 days before operation and stored in CPDA-1 (Fenwal Laboratories, Deerfield, IL) at 4°C. During CPB, whole blood transfusions were given to maintain a hemoglobin level greater than 70 g/L.

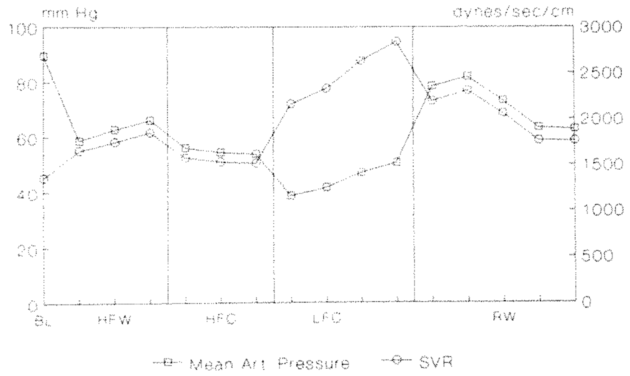


Fig 1. Systemic pressure and vascular resistance (SVR). *(*BL = *baseline;* HFC = *high-flow cold;* HFW = *high-flow warm;* LFC = *low-flow cold;* RW = *rewarming.)*

Measurement of Flow and Temperature

Instantaneous and mean flow of the various arteries was obtained by using a multiplexer (Transonics Systems Inc) that continuously cycled among the flow probes of the four arteries at 15-second intervals. A second single-channel flow meter was used to measure continuous instantaneous and mean extracorporeal flow. Additionally, all flow values were continuously recorded on an

8-channel chart recorder (Hewlett-Packard, Waltham, MA). At each 10-minute data point, temperatures were manually recorded from the temperature probes located in the forebrain, midjejunum, right kidney, right hind limb adductor muscle, and rectum. Arterial and venous blood temperatures during CPB were recorded from the readout of the in-line extracorporeal blood gas monitoring system; the venous temperature from the thermistor port of the Swan-Ganz catheter was recorded when not on CPB.

Measurement of Lactate Levels and Oxygen Consumption

Total body and regional lactate content were determined from arterial and venous samples taken from the left femoral artery and the various appropriate cannulated veins at the designated time points. All analyses were performed in duplicate using a kit (Sigma Chemical Company, St. Louis, MO). Blood samples for lactate, immediately after being withdrawn, were transferred to centrifuge tubes with cold 8% perchloric acid and mixed, and then put back on ice. At the end of the experiment the samples were centrifuged and the supernatant was stored at 4°C until the assay was performed the next morning.

Partial pressures of oxygen and carbon dioxide, and pH, were measured with an IL 1206 blood gas analyzer (Instrumentation Laboratories, Lexington, MA). Percent oxygen saturation, hemoglobin concentration, and oxygen content were determined with an IL 282 Co-Oximeter (Instrumentation Laboratories) with the coefficient selector switch set for canine blood analysis. Oxygen content, oxygen consumption, and oxygen extraction were determined using the equations:

$$O_2 \text{ content} = (\text{Hb} \times 1.34 \times \%O_2 \text{ saturation})/100 + (PO_2 \times 0.003)$$

$$O_2 \text{ consumption} = (CaO_2 - CvO_2) \times (\text{blood flow})$$

$$O_2 \text{ extraction} = (CaO_2 - CvO_2)/CaO_2$$

where Hb is hemoglobin, CaO_2 is arterial oxygen content, CvO_2 is venous oxygen content, blood flow represents organ or total body blood flow (cardiac output or pump flow rate), and PO_2 is oxygen tension. Q_{10}, which is the multiple by which oxygen consumption changes as a result of a 10°C change in tissue temperature, was calculated from the equation [18]:

$$Q_{10} = \text{antilog } (10)(\log VO_{2a} - \log VO_{2b})/(T_a - T_b)$$

where VO_{2a} and T_a are oxygen consumption and temperature at data point a, and VO_{2b} and T_b are oxygen consumption and temperature at data point b. The last data point during the high-flow, warm phase and the first data point during the low-flow, cold phase were used to calculate the Q_{10} for the first half of CPB; the first data point during the low-flow, cold phase and the last data point for the rewarm phase were used to calculate the Q_{10} for the second half of CPB.

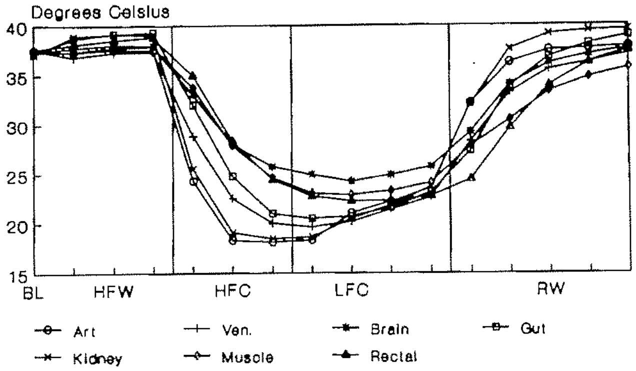


Fig 2. *Regional temperatures. (Abbreviations are the same as in Figure 1.)*

Statistical Analysis

Data for flow, oxygen consumption, oxygen extraction, and lactate levels were analyzed by one-way analysis of variance. Comparison of individual group means to baseline was by Dunnett's multiple range test. Q_{10} values were compared using paired t tests. In each instance, a p value of less than 0.05 was considered to be significant.

Results

Temperatures

The various body organs were noted to cool and rewarm at dissimilar rates and to different final temperatures (Fig 2). The kidney temperatures were almost identical to the arterial temperatures. The jejunum cooled and rewarmed at the next fastest rate, tracking along with the venous temperature. The rectal and muscle temperatures changed at a still slower rate and were roughly similar in value. However, the rectal temperature returned to baseline with 45 minutes of rewarming while the muscle temperature was still several degrees below baseline. The brain cooled and rewarmed at the slowest rate, and was 3° to 4°C warmer than the blood and intraabdominal viscera even during the low-flow, cold period when one would have expected uniform cooling to have been achieved.

Blood Flow

For the purpose of this report, the various organ blood flows mentioned are discussed in the context of *percentage* of pump flow rate or systemic blood flow rate. Blood flow (Fig 3) for the SMA, renal artery, and femoral artery were similar to baseline values during the initial normothermic CPB period while flow to the carotid decreased. With cooling, blood flow to the carotid, SMA, and renal artery progressively decreased to a significant degree, while femoral artery flow significantly increased. When the CPB flow was decreased to 1.5 $L \cdot min^{-1} \cdot m^{-2}$ during the hypothermic period, the percentage of total flow for the carotid artery, SMA, and renal artery increased slightly but was still significantly less than baseline. For the same period, the percentage of total flow for the femoral artery decreased slightly. With rewarming, the femoral arterial flow declined to baseline while the SMA and renal artery

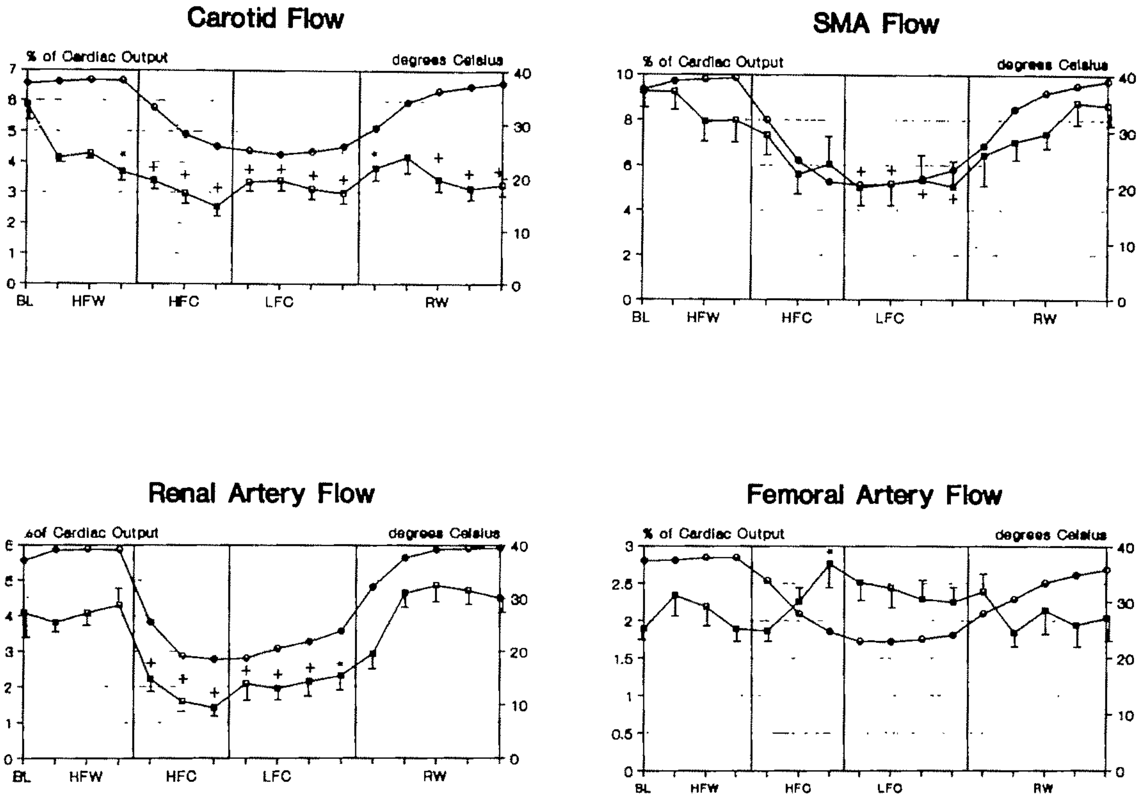


*Fig 3. Flow in various vessels. Squares denote flow, circles denote organ temperature. Error bars represent means ± standard error of the mean. (Significance: *$p < 0.05$, $^+p < 0.01$.) (SMA = superior mesenteric artery; other abbreviations are as in Figure 1.)*

flow increased, returning to baseline. Carotid flow, although not dissimilar to the high-flow, warm values, did not return to the baseline values.

Oxygen Consumption and Extraction

Whole body oxygen consumption (Fig 4) was similar to baseline values during the initial normothermic CPB period. However, whole body oxygen extraction significantly increased with normothermic CPB as the baseline cardiac output for the animals was approximately 4.5 L/min. With cooling, oxygen consumption and extraction declined as expected; with rewarming the whole body oxygen consumption returned to baseline values and whole body oxygen extraction returned to values similar to that seen during the initial high-flow, warm CPB period. The whole body Q_{10} (Table 1) calculated from this was 2.63 for the first half of CPB and 2.56 for the second half of the CPB period.

Brain oxygen consumption (Fig 5), although slightly increased during the high-flow, warm period was not significantly different from baseline values. Brain oxygen extraction (Fig 6) for the high-flow, warm phase, however, roughly tripled in response to the decline in relative total body flow and because the carotid flow as a percentage of the total body flow decreased for the period. With cooling, brain oxygen extraction and consumption declined significantly, and with rewarming they returned to the previous levels seen during the initial normothermic

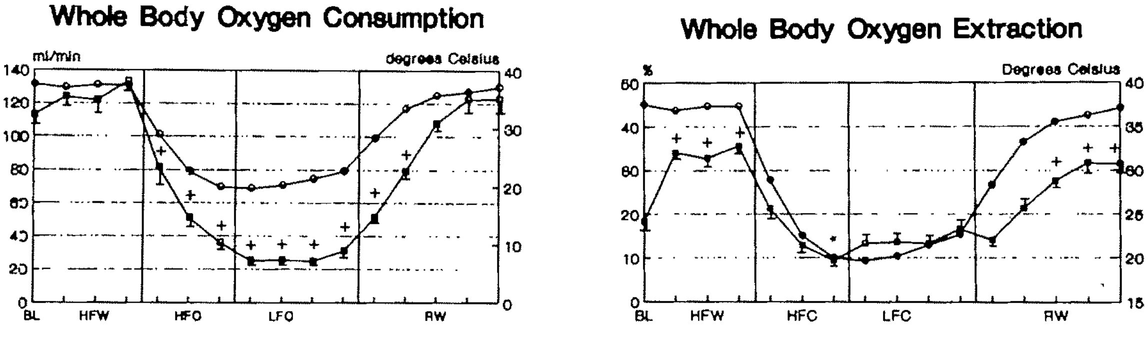


*Fig 4. Whole body oxygen consumption and oxygen extraction (squares). Circles denote venous temperatures. Error bars represent means ± standard error of the mean. (Significance: *$p < 0.05$, $^+p < 0.01$.) (Abbreviations are the same as in Figure 1.)*

Table 1. Systemic and Regional Q_{10} Values

Location	Early CPB	Late CPB	p Value
Body	2.63	2.56	0.27
Brain	4.11	3.73	0.60
Gut	2.83	2.75	0.56
Kidney	2.7	2.61	0.55
Muscle	2.64	2.83	0.30

CPB = cardiopulmonary bypass; Q_{10} = multiple by which oxygen consumption changes as the result of a 10°C change in tissue temperature.

CPB period. The brain Q_{10} derived from this was 4.11 for the first half of the CPB period; it declined to 3.73 for the second half.

Small bowel oxygen consumption at baseline was similar to that measured for the high-flow, warm period, whereas the small bowel oxygen extraction significantly increased for this phase. With hypothermic conditions oxygen consumption and extraction rapidly decreased. Upon rewarming, oxygen consumption for the small bowel returned to baseline. Oxygen extraction at the end of rewarming did not return to those values seen during the high-flow, warm phase although this was not statistically significant ($p = 0.15$). This could be accounted for by the fact that at the end of the rewarming period, small bowel oxygen consumption was slightly less and SMA flow was slightly greater than that seen at the end of the high-flow, warm phase. The small bowel Q_{10} was determined to be 2.83 for the first half of CPB and 2.75 for the second half of the CPB period.

Renal oxygen consumption did not change significantly from baseline to the normothermic period but rapidly decreased with hypothermia. No appreciable decrease in oxygen consumption occurred when the pump flow rate was halved, which suggests that perfusion was adequate during the low-flow period. With rewarming, oxygen consumption increased, but it was significantly depressed compared with baseline and the initial normothermic CPB phase, in spite of kidney temperatures and renal artery flows returning to baseline values. Likewise, the kidney oxygen extraction levels did not return to those levels seen during the initial normothermic CPB phase. The calculated Q_{10} was 2.70 for the first half of the CPB period and 2.61 for the second half.

Muscle oxygen consumption was slightly, but not significantly, higher during the initial normothermic CPB phase as compared with baseline levels. As in the other regions, however, oxygen extraction was significantly increased during this phase. Muscle oxygen consumption declined with hypothermia; with rewarming it increased to values above baseline and the initial normothermic CPB phase, and the difference approached statistical significance ($p = 0.13$). This occurred despite the fact that the muscle temperatures were roughly 2°C below baseline at the end of the rewarming phase. This was reflected in the Q_{10} value, which was 2.64 for the first half of bypass and 2.83 for the second half.

Lactate levels (data not shown) were roughly 2.5 to 3.0 mmol/L at baseline for the various arterial and venous sites. Immediately with the initiation of CPB the measured lactate levels for the various regions uniformly

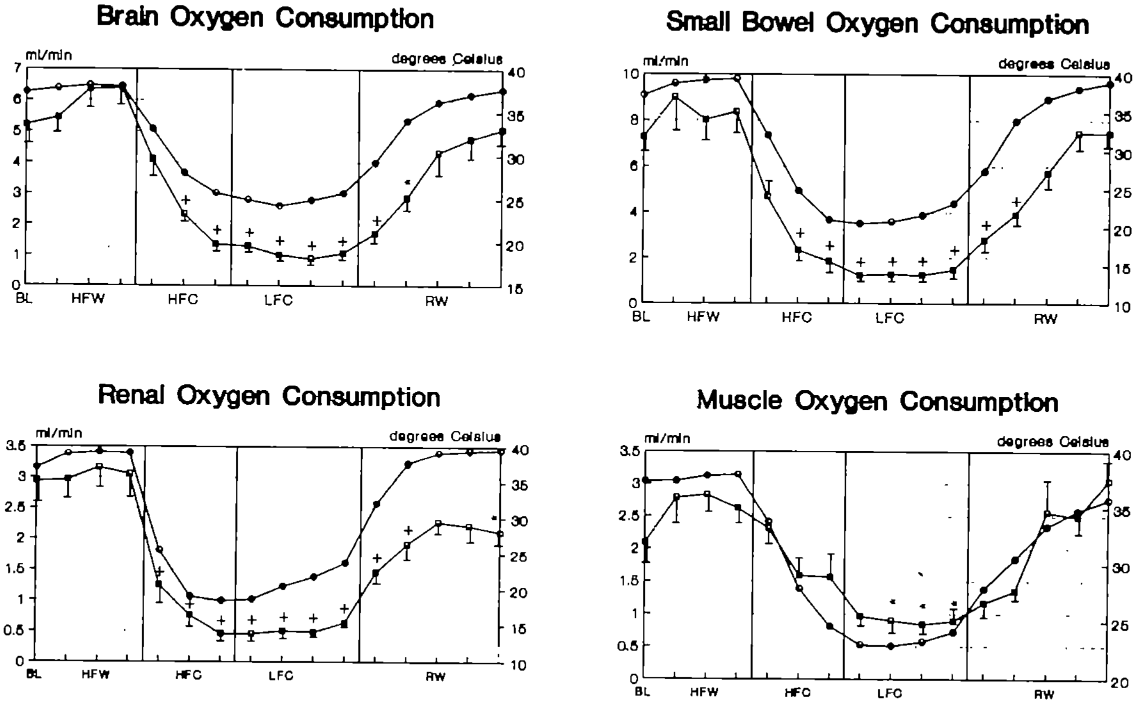
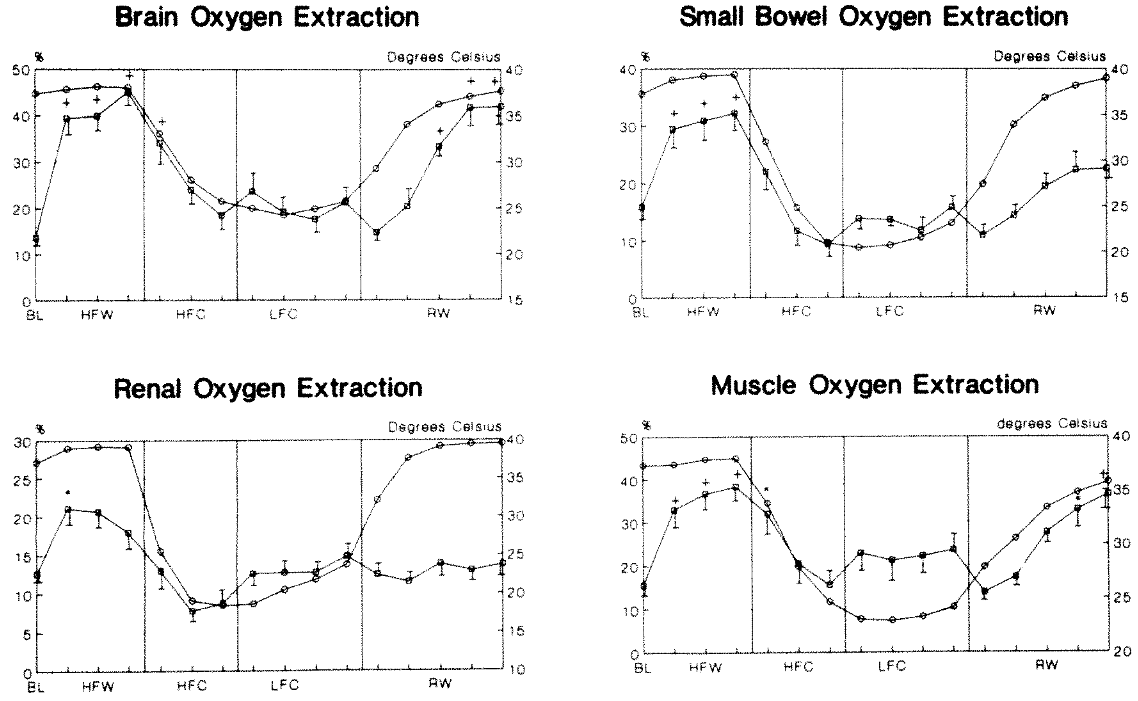


Fig 5. Regional oxygen consumption (squares). Circles *denote organ temperature. Error bars represent means ± standard error of the mean. (Significance:* $^{*}p < 0.05$, $^{+}p < 0.01$.) *(Abbreviations are the same as in Figure 1.)*


Brain Oxygen Extraction

Small Bowel Oxygen Extraction

Renal Oxygen Extraction

Muscle Oxygen Extraction

Fig 6. Regional oxygen extraction (squares). Circles *denote organ temperature. Error bars represent means ± standard error of the mean. (Significance:* $^*p < 0.05$, $^+p < 0.01$.) *(Abbreviations are the same as in Figure 1.)*

increased to 5.5 to 6.0 mmol/L ($p < 0.01$). With the progression of CPB, there was a slow but insignificant rise in the lactate levels such that at the end of the rewarming phase the lactate levels were 6.5 to 7.2 mmol/L. There were no significant differences in lactate levels among the regions at any time point.

Comment

In the present set of experiments we have demonstrated that blood flow to different organ systems is significantly altered during CPB, both during the high-flow, normothermic phase and during hypothermia, at high and low pump flow rates. This altered distribution of blood flow has been noted previously by many investigators [1–9].

We found that during the initial normothermic phase, blood flow declined significantly from baseline levels for the brain but was essentially the same for the intestines, kidney, and skeletal muscle. Many others [1, 2, 7, 14] have noted decreased cerebral blood flow with normothermic CPB. This has been ascribed to microemboli [14, 17], which may be temperature-dependent [14], eg, air emboli. For us this also may have occurred because of the relative slight hypocarbia seen, as our arterial carbon dioxide tensions were unintentionally 5 to 7 mm Hg less during normothermic CPB as compared with baseline values before CPB.

Our finding of proportionally unchanged blood flow to the intestines, kidney, and skeletal muscle during the initial normothermic phase is consistent with aspects of other studies. Splanchnic blood flow during normothermic CPB was found by Rudy and associates [2, 5, 7] to be increased, whereas Mathie and co-workers [4], using an electromagnetic flow probe, determined that portal vein flow was not changed with pulsatile or nonpulsatile CPB. Waldhausen and colleagues [19], in looking at portal vein flow in normothermic CPB, determined that when the pump flow was set at the same as the baseline cardiac output, the portal vein flow was similar to baseline values. When pump flow rates were decreased the portal vein flow also progressively decreased. Lees and associates [1] found that intestinal flow was increased as compared with the awake state but not different from sham controls. Renal and skeletal muscle blood flow during normothermic CPB has been reported to be unchanged [1, 5, 7]. In an experimental model that attempted to separate the individual effects of hemodilution, hypothermia, and the pump-oxygenator during CPB, Utley and co-workers [8] found that during normothermic CPB, hemodilution caused renal cortical blood flow to be increased whereas the pump-oxygenator produced a decrease in renal cortical flow; renal medulla flow was unaffected by either.

During the hypothermic phase of CPB, we observed a progressive temperature-related change in regional blood flow. At 3.0 $L \cdot min^{-1} \cdot m^{-2}$, as the organ temperatures declined the carotid, SMA, and renal artery flows decreased, while the femoral artery flow progressively increased. Teleologically, what we found makes sense: with decreasing metabolic requirements secondary to the progressive hypothermia, blood would be shunted away from the "vital organs" to muscle. Furthermore, skeletal muscle accounts for approximately 40% of the body's mass and its vasodilatory capacity can increase sevenfold to eightfold from its basal level [20]. That blood would be shunted from the brain, intestines, and kidney to the skeletal muscle during high-flow, hypothermic CPB can be deduced from what is known about the various vascular resistances of these organs. Basal tone for the vascular beds of the gastrointestinal tract, kidney, and brain is low, whereas that of resting muscle is 10 to 100 times greater. In studies with a constant high extracorporeal perfusion rate, progressive hypothermia to as low as 15°C produces a progressive decline in blood pressure and systemic vascular resistance [21]. In addition, splanchnic vascular resistance significantly increases with hypothermia but peripheral vascular resistance does not [22].

These findings are confirmed to a large degree by most other studies. Many investigators [6, 7, 9, 13, 14] have found a large decrease in cerebral blood flow with hypothermia and hypothermic CPB. Although this occurs regardless of whether alpha-stat or pH-stat acid-base management is used [6], it is believed [6, 17] that the alpha-stat strategy should be used as it better retains cerebral vascular autoregulation, preventing overperfusion during hypothermia. Similarly, decreased renal artery flow with hypothermia and hypothermic CPB has been shown in several studies [3, 6, 7, 9]. Utley and co-workers [8] determined that hypothermia, independent of the pump-oxygenator or hemodilution, caused decreased renal flow. Increased flow to the skeletal muscle with hypothermia or hypothermic CPB has been seen in some studies [7, 9] but not others [8]. Our study differed from most other studies [7–9] in that with hypothermic CPB we observed a significant decline in intestinal blood flow as opposed to an increase [7–9] or no change [3]. This can be accounted for by several reasons. The microsphere technique for estimation of organ blood flow, which was used in those other studies [3, 7–9], has been found to be in error by 86% to 125% during hypothermia, which may be secondary to increased blood viscosity with hypothermia [3]. The Transonic T101D and T201D ultrasonic flow meter system used in this experiment has an accuracy of ±2% and a reproducibility of ±2%, and is not affected by changes in temperature. Also, in our experiments, we set our flow rate during the high-flow, hypothermic phase at the same rate as during the normothermic phase. In some of the other studies [3, 9] systemic blood flow rate was substantially decreased during hypothermia.

Additionally, we found that with decreasing the pump flow rate from 3.0 $L \cdot min^{-1} \cdot m^{-2}$ to 1.5 $L \cdot min^{-1} \cdot m^{-2}$ and keeping the temperature at a constant level of hypothermia, there was a slight redistribution of organ blood flow. Although the absolute or measured flow value decreased for all four regions with this maneuver, the values as a percentage of total body flow increased slightly for the renal and carotid arteries, was unchanged for the SMA, and decreased slightly for the femoral artery. This would seem to indicate that autoregulation was intact and that perfusion was still adequate at the reduced flow rate.

Whole body oxygen consumption was 118 $mL \cdot min^{-1} \cdot m^{-2}$ at baseline and 121 to 130 $mL \cdot min^{-1} \cdot m^{-2}$ during the high-flow, warm CPB phase, which is similar to other studies [10, 11, 20, 23]. Likewise, brain, intestinal, kidney, and muscle oxygen consumption was similar during the initial normothermic phase as compared with baseline values before CPB. This occurred in spite of the significant increase in oxygen extraction seen during the high-flow, warm phase for all the regions, and in spite of the significantly decreased carotid flow. Oxygen consumption for the body as a whole and for the various organs appropriately decreased as the body was cooled. When the pump flow rate was halved from 3.0 to 1.5 $L \cdot min^{-1} \cdot m^{-2}$, oxygen consumption and extraction did not change significantly for the total body or any of the organ systems, suggestive of as adequate perfusion at the lesser rate as at the higher rate. With rewarming, total body oxygen consumption and extraction returned to high-flow, warm levels. At the regional level, the oxygen consumption values after full rewarming were not significantly different from baseline and high-flow, warm values except in the kidney, where it was significantly less in spite of equal temperature and a slightly greater flow. On the other hand, muscle oxygen consumption at the end of the rewarming phase was higher than baseline and high-flow, warm values despite being roughly 2°C cooler. These results suggest that, although total body oxygen consumption and extraction return to baseline at the end of CPB, it is not necessarily a reflection of oxygen consumption at the regional level. Rather, the return of whole body oxygen consumption to baseline values may be secondary to an increased oxygen consumption of the body's large muscle mass, which may mask a deficient return of oxygen consumption for other organ systems.

Evaluation of Q_{10} values was used to approach this question another way, using temperature as a more prominent factor. By comparing the Q_{10} for the first half of bypass with that of the second half, and assuming that the first Q_{10} represents adequate perfusion, a decrease in Q_{10} would be evidence for a less than adequate level of perfusion. Although there were slight decreases for the brain, kidney, bowel, and total body they were not statistically significant. Likewise, lactate was not a particularly helpful parameter in assessing adequacy of perfusion as the various regions had essentially indistinguishable values. This is probably because it is not rapidly cleared and the assay used had a moderate degree of error. That the lactate levels increase with CPB has been reported [24–26], and may be due to the alkalosis and hypothermia seen with CPB [6, 25]. Additionally, excess lactate (lactate/pyruvate ratio), which we did not measure, is a better index of anaerobic metabolism.

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DISCUSSION

DR JULIE A. SWAIN (Las Vegas, NV): What evidence do you have that common carotid flow, especially in the dog, is proportional to brain flow during various temperatures and flow conditions? Where was the venous catheter positioned for calculation of brain oxygen consumption? Was it in the jugular vein or did you advance it up into the brain? I believe that previous microsphere work has demonstrated that common carotid flows have a substantial contribution of flow to nonbrain structures of the face and skull.

DR LAZENBY: Dr Swain, I will answer the second question first. The venous catheter was placed in the external jugular vein in a cephalad direction and advanced to the root of the skull. In terms of whether the common carotid artery accurately represents flow to the brain in dogs, Wollman and associates [1] discussed this point and concluded that use of the common carotid artery as an index of cerebral blood flow in dogs was valid. I am not familiar with the microsphere data that you are talking about, or at least that aspect of them.

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Coronary Sinus Cardioplegia: Clinical Trial With Only Retrograde Approach

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The cases of 100 consecutive patients who underwent coronary artery bypass grafting with coronary sinus (retrograde) cardioplegia (group R) without the antegrade-retrograde approach were reviewed. To evaluate the safety and the efficacy of this technique, another 100 consecutive patients who underwent a similar procedure but with conventional aortic root (antegrade) cardioplegia (group A) were used as a comparison. The two groups were similar with respect to age, male to female ratio, associated medical problems, extent of coronary artery disease, mean preoperative ejection fraction (0.56 ± 0.13 versus 0.53 ± 0.18), pump time (113.1 ± 43 versus 111.7 ± 38 minutes), aortic cross-clamp time (57.4 ± 20 versus 60.8 ± 23 minutes), number of grafts per patient, level of hypothermia, complication rate, rate of postoperative myocardial infarction (4% versus 3%), and mortality rate (2% versus 2%). Hemodynamic measurements were made 6 hours after operation in 59 patients in group R and 47 patients in group A. The cardiac index, left ventricular stroke work index, and right ventricular stroke work index were better in group R but not significantly so ($p > 0.05$). However, only 27% of patients in group R required a temporary pacemaker, and only 9% needed inotropic agents after 6 hours of operation in contrast to 51% and 42%, respectively, in group A ($p < 0.05$). There were no complications from catheter intubation. In group R, right ventricular wall temperature (11° ± 3.6°C) was higher than the septal (10.8° ± 3.2°C) and left ventricular wall temperatures (9.1° ± 2.8°C) ($p > 0.05$). Cardioplegia delivery through the coronary sinus alone is safe for clinical use. The technique is simple, provides homogeneous myocardial cooling, and could be a better method of achieving cardioplegia in patients undergoing coronary artery bypass grafting.

(Ann Thorac Surg 1992;53:965–71)

Retrograde cardioplegic protection of the myocardium has received rapidly increasing interest from cardiac surgeons. Its appeal stems from the known limitations of antegrade delivery of cardioplegia, namely, inadequate distribution of cardioplegia distal to the coronary artery obstructive lesion, damage to coronary artery ostia, difficulty in ostial cannulation, and distal emboli from the previous vein graft.

Retrograde cardioplegia could provide better myocardial protection despite the coronary lesions [1, 2]. Coronary ostia are neither sought nor injured with retrograde methods. The old vein graft can be cut, and distal emboli can be flushed retrogradely out of the coronary artery and vein graft. Moreover, reoperation with patent internal mammary arteries is less risky because all parts of the heart receive adequate myocardial protection from retrograde perfusion. Despite these obvious benefits, the principal limitation of retrograde cardioplegia in the past has been the complicated steps required to cannulate the coronary sinus, including atriotomy, bicaval cannulation, and caval snaring. A recent limitation is the difficulty of intubating the coronary sinus through the right atrium.

The clinical use of retrograde cardioplegia still raises some concerns, including potentially inadequate preservation of the right ventricle and delay in stopping the heart with slow retrograde perfusion. Also, the combined antegrade-retrograde approach may have some advantages over retrograde cardioplegia alone [3]. Therefore, at present, most surgeons are in favor of the combined approach [4, 5]. However, this technique has some disadvantages. It requires another set of tubing on the operating table or other equipment for the perfusionist to be able to switch back and forth from one type of perfusion to the other [4]. Using this technique could be cumbersome, confusing, and more time-consuming while the aorta is cross-clamped. If retrograde cardioplegia alone proves to be effective, providing good myocardial protection and safety for clinical use, it could become a technique of choice for myocardial protection in the future.

In an effort to better define the role of retrograde cardioplegia, we compared two groups of patients undergoing a coronary artery bypass procedure with either antegrade (aortic root) or retrograde (coronary sinus) cardioplegia.

Material and Methods

The cases of 100 consecutive patients with coronary artery disease who were operated on at our institution between November 1989 and October 1990 were reviewed. All of these patients received retrograde cardioplegia (group R) through the coronary sinus alone, without the antegrade-retrograde approach, for myocardial protection during

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aortic cross-clamping. To evaluate the safety and efficacy of this technique, another 100 consecutive patients who underwent coronary artery bypass grafting by the same surgeons at the same institution during the period between November 1988 and October 1989 were used for comparison. All of these patients had conventional aortic root cardioplegia, or the antegrade approach (group A).

All patients had major coronary artery disease and underwent operation on either an elective or emergency basis. Before operation, 86% of the patients had a pulmonary artery balloon-tipped catheter inserted, and all had radial artery lines for hemodynamic monitoring. After general anesthesia and sternotomy, ascending aortic and atrial cannulas were used to establish cardiopulmonary bypass. The details of cardiopulmonary bypass have been described elsewhere [6].

Cold crystalloid cardioplegia with 25 mEq/L of potassium chloride was delivered as soon as the aortic cross-clamp was applied. Moderate systemic hypothermia (28° to 30°C) and topical hypothermia with cold saline solution were used in every patient. In 64% of the patients in group R and 37% in group A, the myocardial temperature was measured as soon as diastolic arrest was completed after the first dose of cardioplegia. A temperature probe was placed at the septum, left ventricular wall, and right ventricular wall in group R, but only in the septum in group A.

In group A, an initial bolus of 500 to 700 mL of cardioplegic solution was used followed by an intermittent dose of 200 mL every 20 minutes during aortic cross-clamping. The same approach was carried out in group R except a larger bolus of 1,000 mL was given directly into the coronary sinus during a 2- to 3-minute period while coronary sinus pressure was maintained at less than 60 mm Hg. No additional doses of cardioplegia were given through the vein grafts after completion of the distal anastomoses in either group. The details of transatrial coronary sinus cardioplegia delivery have been described elsewhere [7]. In both groups, hemodynamic measurements were obtained just before initiation of cardiopulmonary bypass and repeated approximately 6 hours later, when the hemodynamic instability was corrected. Arterial blood pressure, heart rate, central venous pressure, pulmonary artery pressure, and pulmonary wedge pressure were recorded. Cardiac output determinations were made with an American Edwards Laboratories Swan-Ganz catheter and computer (Santa Ana, CA).

The cardiac index, stroke volume, systemic vascular resistance, pulmonary vascular resistance, right ventricular stroke work index, and left ventricular stroke work index were derived. The hemodynamic measurements were made 5 to 7 hours after the cessation of cardiopulmonary bypass when pulmonary wedge pressure was at or close to 15 mm Hg. An electrocardiogram and serum enzyme levels were obtained on arrival in the intensive care unit and on a daily basis thereafter. These variables were measured in all patients; however, only 47 patients in group A and 59 patients in group R reached a pulmonary wedge pressure of 15 mm Hg at the time the measurements were done.

Table 1. Patient Profile by Group[a]

Variable	Antegrade Group (n = 100)	Retrograde Group (n = 100)
Sex	75 men, 25 women	72 men, 28 women
Age (y)	64.10 ± 11.3	63.35 ± 10.3
Preop COPD	4	4
Preop diabetes	9	20
Preop hypertension	52	45
Abnormal BUN (>20 mg/100 mL)	23	17
Abnormal creatinine (>1.5 mg/100 mL)	10	7
Preop MI	47	46
Preop IABP	10	14
Ejection fraction	0.56 ± 0.13	0.53 ± 0.18
Pump time (min)	113.12 ± 43.1	111.71 ± 37.8
Cross-clamp time (min)	57.41 ± 19.5	60.83 ± 22.7
Grafts per patient	3.11	3.61
LIMA used	65	66
Operative mortality	2	2
Postop MI	4	3
Postop pacemaker	51	27[b]
Postop peak CK-MB (ng/mL)	67.15 ± 76.9	58.35 ± 62.7
Postop atrial arrhythmias	45	49
Postop inotropic agents (after 6 h)	42	9[b]

[a] Where applicable, data are shown as the mean ± the standard deviation.
[b] Significance: $p < 0.05$.

BUN = blood urea nitrogen; CK-MB = myocardial-specific isoenzyme of creatine kinase; COPD = chronic obstructive pulmonary disease; IABP = intraaortic balloon pump; LIMA = left internal mammary artery; MI = myocardial infarction.

The data were analyzed both as absolute values and as percentages of base values and were expressed as the mean and standard deviation. For discrete variables, comparisons were made with χ^2 analysis. A p value of less than 0.05 was considered significant.

Results

The two groups were similar with respect to age (64 ± 11 versus 63 ± 10 years), associated medical problems, angiographic extent of coronary artery disease, mean preoperative ejection fraction (0.56 ± 0.13 versus 0.53 ± 0.18), and preoperative instability requiring intraaortic balloon insertion. There was no difference in the incidence of postoperative renal or pulmonary complications. There was no significant difference in the peak level of the myocardial-specific isoenzyme of creatine kinase (67 ± 77 versus 58 ± 63 ng/mL) or in the incidence of postoperative myocardial infarction (4% in group A and 3% in group R). The operative mortality was 2% in both groups (Table 1).

There was a significant difference between the two

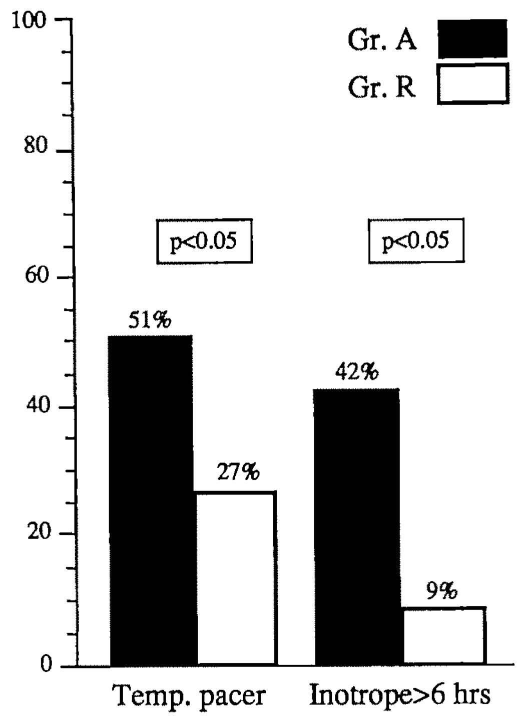

Fig 1. Comparison of postoperative requirements of temporary pacemaker and inotropic agents in the antegrade cardioplegia group (Gr. A) *and the retrograde cardioplegia group* (Gr. R). *Group R required fewer pacemakers and less inotropic agents after operation* ($p < 0.05$).

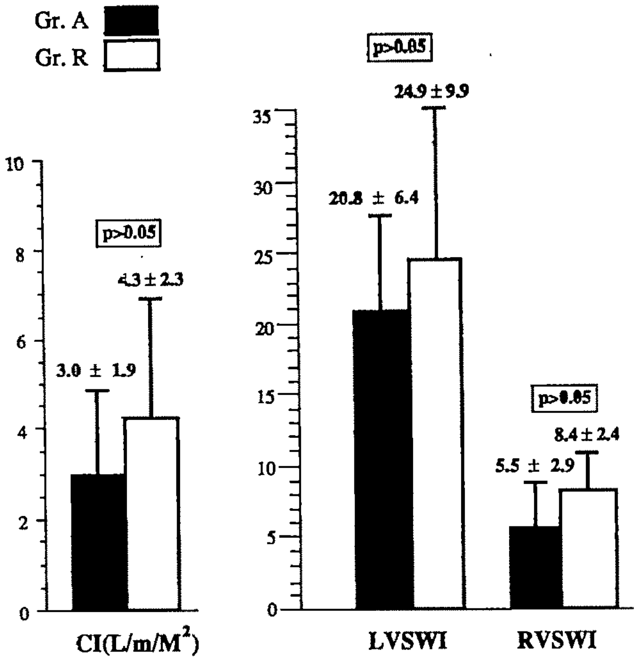

Fig 2. Postoperative cardiac index (CI), *left ventricular stroke work index* (LVSWI), *and right ventricular stroke work index* (RVSWI). *There were 59 patients in the retrograde cardioplegia group* (Gr. R) *and 47 in the antegrade cardioplegia group* (Gr. A). *The LVSWI and RVSWI were measured in gram-meters per square meter at a pulmonary capillary wedge pressure of 15 mm Hg. There is a trend showing that at 6 hours after operation, the results of hemodynamic studies were better in group R, but the differences did not reach significance* ($p > 0.05$).

groups in the number of patients requiring temporary pacemaker wires after coming off cardiopulmonary bypass, the percentage being significantly lower in group R (27% versus 51%). Also, the number of patients requiring inotropic agents after 6 hours of operation was significantly lower in group R (9% versus 42%) (Fig 1).

Studies using a pulmonary catheter to record and compute the hemodynamic variables showed that there was a difference in cardiac index (3.0 ± 2 versus 4.3 ± 2 $L \cdot min^{-1} \cdot m^{-2}$), left ventricular stroke work index (21 ± 6 versus 25 ± 10 g-m/m^2), and right ventricular stroke work index (5.5 ± 3 versus 8.4 ± 2 g-m/m^2) at a fixed preload of 15 mm Hg (mean right atrial pressure, 11 ± 3 mm Hg, mean pulmonary artery pressure, 24 ± 5.5 mm Hg; and mean aortic pressure, 70 ± 18 mm Hg). It appears that the group receiving retrograde cardioplegia may have had better cardiac output, left ventricular stroke work index, and right ventricular stroke work index, but the difference did not reach significance (Fig 2).

Comment

Retrograde coronary perfusion through the coronary sinus was first used by Pratt [8] in 1898 as a means of myocardial preservation. Pratt theorized that myocardial blood supply is maintained not only by coronary artery blood flow but also by blood flow in the thebesian veins and backflow in the coronary veins. In 1940, Beck used retrograde perfusion to deliver blood to the coronary venous system by way of a graft from the aorta. This did not support the beating functioning heart, but it did bring attention to the use of retrograde perfusion [9]. Lillehei and colleagues [10] in 1956 reported the use of retrograde perfusion of oxygenated blood during an aortic valvotomy for critical aortic stenosis. However, the utilization of retrograde perfusion was suppressed with the reintroduction of antegrade cardioplegia and hypothermia during the mid-1970s.

To understand retrograde perfusion of the coronary sinus, the anatomy of the coronary veins needs to be emphasized. Recently, excellent details have been provided by Tschabitscher [11], Ludinghausen [12], and Hochberg and Austen [13]. There are two systems that return coronary blood to the heart: (1) the greater cardiac venous system and (2) the lesser cardiac venous system. The greater cardiac venous system is variable. Its major and more constant components are the coronary sinus, the great cardiac vein, the anterior ventricular (anterior cardiac) vein, the posterior vein of the left ventricle, the posterior interventricular (middle cardiac) vein, the oblique vein of Marshall, and the small cardiac vein. The lesser cardiac venous system is composed of the small thebesian veins, which are venous or sinusoidal connections to cardiac chambers; they drain primarily the septum, the conus of the right ventricle, and the lateral walls of the atria.

Approximately 75% of the venous return is through the greater cardiac venous system and through the coronary sinus, and the remainder is through the lesser cardiac venous system. Moreover, up to 5% of the venous return may drain directly into the left ventricle.

The greater cardiac venous system is also a part of the subepicardial venous plexus with flow toward the coronary sinus. This extensive network is the basis for retrograde protective methods during operation. In addition, the transmural venous network is arranged subepicardially and communicates with the cardiac venous system. This transmural venous network comprises intramyocardial veins, postcapillary venules, and thebesian veins. It is a huge network throughout the myocardium that communicates freely with the subepicardial venous plexus. This tremendous communication between subepicardial and transmural venous channels has a major role in transmitting the cardioplegic solution infused into the coronary sinus and great cardiac vein throughout the entire myocardium. These anatomical features support the concept that the right side of the heart can be adequately cooled and protected with cardioplegic solution when the catheter is in the distal end of the coronary sinus and great cardiac vein, without the need of antegrade cardioplegia. Moreover, the right atrium and the right ventricle may be cooled by cold cardioplegic solution that egresses from the myocardium into the right atrium and right ventricle through the thebesian veins and capillary veins.

Of interest is the fact that retrograde perfusion of the myocardium by way of the coronary sinus is accomplished despite the frequent presence of valves in some of the veins. Usually the great cardiac vein has two valves at its mouth at the coronary sinus, and often small tributaries from the left atrium and ventricle have valves at their junctions with the great cardiac vein. The middle cardiac (posterior interventricular) vein usually has a single valve near its opening into the coronary sinus. Valves normally are not found in other named cardiac veins.

Combined antegrade-retrograde cardioplegia has been proposed to be better than retrograde cardioplegia alone to preserve the myocardium during aortic cross-clamping for two major reasons. One is that retrograde cardioplegia alone could delay rapid cardiac arrest and may necessitate a larger volume than antegrade infusion, and the other is that retrograde cardioplegia could result in inconsistent right ventricular cooling and recovery [3, 4].

In retrograde myocardial protection, preservation of the right ventricle is a critically relevant issue because it is now well recognized that right ventricular dysfunction can occur after cardioplegic arrest and, in some cases, adversely affects the postoperative outcome [14, 15]. In fact, concerns about the ability of coronary sinus cardioplegia to preserve right ventricular function have been raised primarily on the basis of experimental canine studies showing that injection of a low-viscosity resin into the coronary sinus results in poor perfusion of the right ventricular free wall and of the interventricular septum. However, the drainage flow patterns of these anatomical structures are more favorable in humans than in dogs [16, 17].

Three recent articles reported three different techniques, and the results suggest that right ventricular function is well preserved after coronary sinus cardioplegia. Menasché and associates [18] used technetium 99m–labeled red cells to assess global and segmental right ventricular function. They concluded that coronary sinus cardioplegia alone for coronary artery bypass and valve operations did not result in postoperative abnormalities of new onset in any of the three anatomically defined right ventricular regions, ie, free wall, apex, and septum. Eichhorn and co-workers [19] randomized 20 patients to receive either antegrade or retrograde cardioplegia while right ventricular volume and performance were observed. There was a trend for the antegrade group to increase right ventricular end-diastolic volume ($p < 0.1$), whereas the retrograde group had no change in this variable from the preoperative state. The postoperative left ventricular function curve suggested equivalent systolic performance in both groups. Gundry and colleagues [1] observed intraoperative transesophageal echocardiography of right ventricular function before and after bypass in 40 patients undergoing valve or valve and revascularization procedures with retrograde cardioplegia alone. All patients studied had preserved or improved right ventricular function before chest closure.

A substantial number of experimental studies indicate that retrograde cardioplegia may be safe and possibly more effective than aortic root methods. Wechsler and colleagues [20] showed that retrograde cardioplegia preserves high-energy phosphate levels as well as antegrade cardioplegia. Engelman and co-workers [21] also demonstrated that the levels of carintine, acetylcoenzyme A, adenosine triphosphate, and beta-oxidation metabolites are similar in both retrograde and antegrade cardioplegia. Retrograde cardioplegia has been shown to provide more uniform cooling in the presence of coronary artery obstructive disease than antegrade cardioplegia. In those studies [22, 23], myocardial temperatures were similar in both cardioplegia infusion methods and took the same time for cardiac arrest. Horneffer and associates [24] showed experimentally that oxygenated retrograde crystalloid cardiolegia may provide the best method for myocardial protection after ischemia and subsequent reperfusion injury.

Studies in patients undergoing coronary artery bypass grafting have corroborated the notions derived from experimental work. Several of these studies [18, 25] suggested that retrograde perfusion during aortic valve replacement is an excellent alternative when ostial cannulation would otherwise be necessary. Using thermographic techniques, Shapira and associates [26] found more uniform cooling in the flow-restricted regions of patients with coronary artery disease when retrograde cardioplegia was used. Menasché and co-workers [18] found that retrograde cardioplegia provided postoperative left ventricular function equal to that of traditional antegrade methods and suggested coronary sinus cardioplegia remain the method of choice for patients with aortic insufficiency, patients having lengthy multiple valve or combined procedures, and patients having aortic root procedures.

Recently, both Fabiani and colleagues [27] and Bloom and associates [28] found that retrograde cardioplegia was safe for elective coronary bypass operations. At about the same time, Guiraudon and co-workers [29] found retrograde cardioplegia effective in coronary bypass procedures but not superior to the antegrade method for preserving function of the left ventricle. Despite excellent experimental and clinical studies, they concluded that no large clinical study has shown clearly that retrograde cardioplegia ensures better myocardial protection than the current aortic root method.

A larger group of patients was carried in our study. The study, however, was not intended to compare the difference between the antegrade-retrograde approach and retrograde cardioplegia, but rather to compare the conventional standard technique of antegrade cardioplegia with retrograde cardioplegia through direct cannulation of the coronary sinus.

The study was not performed in a blinded fashion, but the patients were all consecutive, and both elective and urgent coronary artery bypass procedures were included. The ages of the patients and all preoperative conditions, including ejection fraction and preoperative requirement of an intraaortic balloon, were comparable between groups A and R. There was no difference in cross-clamp time, number of grafts per patient, or myocardial temperature between the two groups. In group A, myocardial temperature was recorded only in the septum. The septal temperature ranged from 5° to 16°C (mean temperature, 11.8° ± 5.8°C). Homogeneous cooling was observed in group R; spot temperature checking right after the first cardioplegic dose showed that the left ventricular wall, right ventricular wall, and septal temperatures were 9.1° ± 2.8°C, 11° ± 3.6°C, and 10.8° ± 3.2°C, respectively ($p > 0.05$). This finding supports the notion of Gundry and others that the right heart could be cooled through the transmural venous plexus communication and endocardial topical cooling of egressed solution.

There was no significant difference in postoperative morbidity and mortality between the two groups. However, the number of patients requiring inotropic medication (dobutamine hydrochloride or dopamine hydrochloride) after 6 hours of operation was significantly less in group R (42% versus 9%). The majority of patients who received inotropic agents later required sodium nitroprusside infusion. Also, at the time of operation, the right and left ventricles appeared to have more vigorous contraction in group R, with the majority of patients (73%) requiring no temporary pacing. In contrast, about 50% of the patients who had antegrade cardioplegia had some degree of heart block and required pacing at the time they left the operating room. Why group R needed less temporary pacing is not known. However, one of the mechanisms for the development of conduction defects is ischemic injury to the specialized conduction system with cardioplegic arrest. In this particular situation, homogeneous cooling with retrograde cardioplegia may provide better protection to the conduction system. In general, new conduction defects are a known complication of myocardial infarction. In our study, new postoperative conduction defects were no more frequent in patients with postoperative myocardial infarction in both groups.

Thermodilution cardiac output was carried out between 5 and 7 hours after operation. At the time, the patients were in more stable condition and had a left ventricular filling pressure of greater than 12 mm Hg. A pulmonary wedge pressure of 15 mm Hg was chosen as a reference point to obtain meaningful comparable data, but only 47 patients in group A and 59 patients in group R had a pulmonary wedge pressure of 15 mm Hg when the cardiac output study was undertaken. Cardiac index and stroke work index were therefore computed from these patients only. The data suggest that retrograde cardioplegia could provide better postoperative ventricular function, but the difference did not reach significance.

In summary, good clinical results can be obtained in patients who undergo coronary artery bypass grafting with antegrade or retrograde cardioplegia. The results appear to favor the retrograde approach. Combined antegrade-retrograde cardioplegia has also been shown to be effective, but this method could be cumbersome and confusing during the adjustments of the flow clamps for antegrade and retrograde delivery. Retrograde cardioplegia alone is simple and effective. It provides adequate myocardial protection and cooling of the right ventricle, and it could be a better method of myocardial preservation.

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DISCUSSION

DR TIMOTHY J. GARDNER (Baltimore, MD): Dr Arom, I enjoyed your excellent presentation but believe that one must be fairly critical of this kind of clinical series. You stated that retrograde cardioplegia has obvious benefit, and you associated retrograde cardioplegia with better myocardial protection. I do not believe, however, that this study, well conducted as it was, proves your implied contention that retrograde cardioplegia is a superior method for myocardial protection. Most of us believe that our own tailored techniques of myocardial preservation are quite good. If we polled any group of practicing cardiac surgeons, we would find great variations in protective techniques, but we would also note that most believe the techniques we have evolved are very good and quite satisfactory.

I do not think that you proved with this series of patients that retrograde cardioplegia for routine use is in any way better than many other available techniques. You used as an indicator of benefit a reduced need for inotropic support, yet you had normal or statistically similar indices of cardiac function between the two groups. Furthermore, there are many factors that can have an impact on the subjective assessment of when a patient needs inotropic drug use, such as the state of peripheral vascular resistance. What I believe you did show with these patients is that retrograde cardioplegia can be used safely and effectively, that it is relatively simple in your hands, and that it is one of several options available today for achieving good myocardial protection.

A much more important point regarding retrograde cardioplegia may be the one alluded to by Noel Mills in his presentation at the Postgraduate Course, namely, there may be some very specific indications for use of retrograde cardioplegia. One example is a patient with severely atherosclerotic grafts and native coronary arteries who requires a coronary reoperation. An important point is that if we do not obtain some familiarity with the technique of coronary sinus cannulation, we might not have this option available for use in such patients.

DR HOOSHANG BOLOOKI (Miami, FL): I take issue with the previous discussant in that my colleagues and I like to use retrograde cardioplegia routinely for all our patients, not just select patients or those undergoing coronary bypass procedures. Dr Mark Alkire, who was our resident last year and now practices in Tampa, analyzed our results in more than 100 consecutive patients, 55% of whom had procedures other than coronary bypass including valve procedures, aortic dissection, complicated emergency procedures, and mapping operations. We were successful in achieving retrograde cardioplegia in more than 93% of patients. We use this technique because it is convenient and safe. Our results have been excellent with a mortality rate of only 3% in this diverse group, and the ventricular performance postoperatively has been as good as when we use antegrade cardioplegia.

I have a mathematical question. The hemodynamic values that you presented, although they are computer derived, show a low mean stroke work index of 20 ± 24 g-m/m^2 for the left ventricle and similarly a low stroke work index for the right ventricle. These data, I believe, were derived in the early postoperative period when patients were receiving pressor agents. Unless you deliberately keep your patients somewhat hypotensive and allow a fast heart rate, at a mean pulmonary wedge pressure of 15 mm Hg, the stroke work index values should be more than 25 g-m/m^2, especially if the cardiac index is abnormally high. In fact, a stroke work index of 20 g-m/m^2 and a mean pulmonary wedge pressure of 15 mm Hg border the definition of cardiogenic shock by our criteria [1].

In addition, by our criteria, if these data were calculated when the patients were receiving moderate or high doses of pressor agents, then some of them may have been in need of temporary intraaortic balloon pump support. Were there any problems with data entry into the computer, or do you like to keep your patients hypotensive with peripheral vasodilatation after the operation? These factors will lead to the mathematical calculation of a low left ventricular stroke work index in spite of a satisfactory cardiac index and warm and dry extremities.

DR AROM: Thank you, Dr Gardner, for your comments. I pretty much agree with what you said. As we know, there is no absolute information available at present to prove that the antegrade approach is better than the retrograde approach or that the retrograde approach is better than the combined antegrade-retrograde approach and vice versa. However, we have now learned that the retrograde technique alone is simple, is easy to use, and could provide an alternative technique for myocardial protection in coronary artery bypass operations.

As far as Dr Bolooki is concerned, I am pleased to hear that you like the retrograde approach. I am not quite sure that I can answer your question entirely at this point. We kept patients on a regimen of dobutamine hydrochloride and nitroglycerin. Therefore, the mean arterial pressures were between 62 and 75 mm Hg, and the heart rate ranged between the high 80s and middle 120s. Using a thermodilution catheter, the cardiac outputs were measured, and the stroke volume and stroke work indices were computed. The cardiac outputs were adequate, even when the stroke volume and stroke work index were on the low side, but did not reach any level of cardiogenic shock, as concerned you. These findings were also supported by the clinical observation that all the patients were warm with good perfusion and excellent urine output. As you know, high heart rate and low mean aortic and pulmonary artery pressures will give a low stroke volume and stroke work indices in spite of adequate cardiac output.

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Esophageal Carcinoma: Esophageal Ultrasound Assessment of Preoperative Chemotherapy

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The effect of preoperative chemotherapy in the treatment of esophageal carcinoma is difficult to assess because of the inadequacies of clinical staging. Endoscopic esophageal ultrasound (EUS) has been shown to be accurate in the clinical determination of depth of tumor invasion (T) and regional lymph node status (N). Therefore, EUS may be useful in assessing the effect of preoperative chemotherapy in the treatment of esophageal carcinoma. Eleven patients with operable adenocarcinoma of the esophagus or esophagogastric junction underwent staging by EUS before treatment. This was followed by two courses (10 patients) or one course (1 patient) of chemotherapy: etoposide, 120 mg/m^2 for 3 days; doxorubicin hydrochloride, 20 mg/m^2; and cisplatin, 100 mg/m^2. Restaging by EUS was done after treatment. Ten patients then underwent resection of the tumor with lymphadenectomy. One patient was found to have metastatic disease at thoracotomy and did not undergo resection. However, tissue sampling was adequate for the determination of pathological stage. Independent pathological determinations of T and N were then obtained. On completion of chemotherapy, 9 patients (82%) had relief or reduction of preoperative symptoms, and 9 patients (82%) had either no evidence of tumor or reduction of tumor size by endoscopy. Despite this clinical and endoscopic response, no patient had EUS–documented and pathology-confirmed reduction of T. However, 2 patients had EUS–documented and pathology-confirmed progression of N. The accuracy of EUS in the determination of T was 82% and of N, 73%. We conclude that EUS offers a unique evaluation of the esophageal wall and adjacent tissue and is superior to symptomatic or endoscopic assessment of the effect of preoperative chemotherapy in the treatment of esophageal carcinoma.

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The staging of malignancies has improved with advancements in the diagnosis and treatment of cancer. The stage of a tumor can be determined by diagnostic evaluation before treatment (clinical staging) or by evaluation of the resected specimen (pathological staging). Accurate pathological staging is crucial for the prognosis, management, and study of patients after resection. Clinical staging, although less precise than pathological staging, is critical in the selection of appropriate treatment [1]. In addition, clinical staging provides an objective means for assessing the response to various agents in controlled trials of multimodality therapy [2, 3]. Previous studies [4–7] have used relief of preoperative symptoms, barium esophagram, esophagoscopy, or computed tomographic scan (CT) to assess the clinical stage before and after treatment and to evaluate the degree of response of esophageal carcinoma to preoperative therapy. However, the accuracy of these clinical staging techniques in predicting the pathological stage is not optimal.

The recent introduction of endoscopic esophageal ultrasound (EUS), an advancement in the staging of esophageal carcinoma, has prompted the introduction of a new staging system for esophageal carcinoma. This current staging system was developed by the American Joint Committee on Cancer (AJCC) [8] in conjunction with the International Union Against Cancer [9] and uses the TNM format. T characterizes the primary tumor by measuring the depth of invasion of the esophageal wall by the primary tumor; N characterizes the regional lymph nodes by assessing them for the presence of metastases; and M characterizes sites of potential distant metastatic disease. The TNM sets are then arranged into staging groups that rank tumors from those with the best prognosis (stage 0) to those advanced tumors with the worst prognosis (stage IV). The staging is as follows:

T: Primary Tumor
  TX Primary tumor cannot be assessed
  T0 No tumor
  Tis Carcinoma in situ
  T1 Tumor invades the lamina propria or submucosa
  T2 Tumor invades the muscularis propria
  T3 Tumor invades the periesophageal tissue
  T4 Tumor invades adjacent structures
N: Regional Lymph Nodes
  NX Regional nodes cannot be assessed
  N0 No regional lymph node metastases
  N1 Regional lymph node metastases

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M: Distant Metastases
MX Distant metastases cannot be assessed
M0 No distant metastases
M1 Distant metastases

Staging Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
	T3	N0	M0
Stage IIb	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Esophageal ultrasound enables the endoscopic placement of a high-frequency ultrasound transducer in close proximity to the esophageal wall and periesophageal tissues. The esophageal wall is imaged as a five-layered structure by EUS, allowing depth of tumor invasion (T) to be assessed. This technique also provides a unique visualization of regional lymph nodes (N). Size, shape, margin, and echo characteristics can be evaluated. The celiac axis lymph nodes, now considered a site of distant metastases (M), can also be visualized. Several recent prospective studies [10–13] have demonstrated that clinical determination of T and N of esophageal cancer with EUS is superior to CT. Therefore, EUS may be a more accurate means of assessing the therapeutic effect of preoperative chemotherapy in the treatment of esophageal carcinoma.

Material and Methods

Thirteen patients with carcinoma of the esophagus constituted the study cohort, and 11 completed the study. All patients were men. Age ranged from 50 to 69 years (median age, 60 years; mean age, 60.7 years). The presence of biopsy-proven adenocarcinoma of the esophagus or esophagogastric junction with no clinical evidence of distant metastatic disease (beyond the celiac axis), medical suitability for esophageal resection, and an Eastern Cooperative Oncology Group performance status of 0 to 2 were the eligibility criteria. Patients who had received any previous therapy for the malignancy or who had any evidence of major preexisting renal or hematological dysfunction were excluded. All patients were assessed by a thoracic surgeon, a gastroenterologist, and a medical oncologist. This study was approved by the Cleveland Clinic Foundation Research Programs Committee (November 21, 1987), and appropriate informed consent was obtained before treatment was begun.

Pretreatment staging evaluation included a medical history, physical examination, complete blood count, electrocardiogram, urinalysis, and serum chemistry tests including urea nitrogen, creatinine, calcium, phosphorus, alkaline phosphatase, serum glutamic-oxaloacetic transaminase, lactate dehydrogenase, albumin, total protein, bilirubin, and uric acid. All patients underwent baseline barium esophagraphy, chest radiography, CT of the chest and abdomen, and pulmonary function studies. Bronchoscopy was performed only when indicated by the extent or location of the primary lesion.

Esophagogastroduodenoscopy, endoscopic esophageal biopsy, and endoscopic EUS were performed in all patients. Patients were premedicated with meperidine hydrochloride, 50 mg, and midazolam hydrochloride, 2 mg, intravenously. Local anesthesia was not required. During the upper gastrointestinal endoscopy study, biopsy specimens of the tumor were obtained for pathological confirmation in all 13 patients (8 had Barrett mucosa). An Olympus EU-M3 ultrasound endoscope (Olympus Corporation, Lake Success, NY) was passed blindly and positioned endoscopically to examine the entire esophagus, upper portion of the stomach, adjacent segment of the liver, and celiac axis. The examinations were videotaped. Using the AJCC staging system, the pretreatment clinical determination of T and N was recorded [14]. When possible, adjacent sites of metastases were studied, and an attempt was made to define the status of distant metastatic sites (M) by EUS. Patients with T1–4 N0–1 M0–1 (M1 = celiac lymph node metastases only) disease were eligible for preoperative therapy.

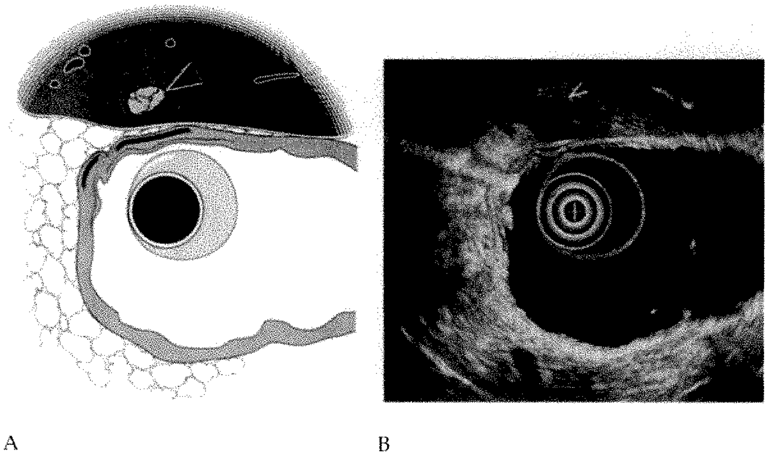

Fig 1. (A) A hepatic metastasis (arrow) *in the left lateral segment of the liver. The esophageal ultrasound probe is seen in the gastric cardia. (B) The hepatic metastasis* (arrow) *as seen from the gastric cardia by esophageal ultrasound. The metastasis was imaged only by esophageal ultrasound.*

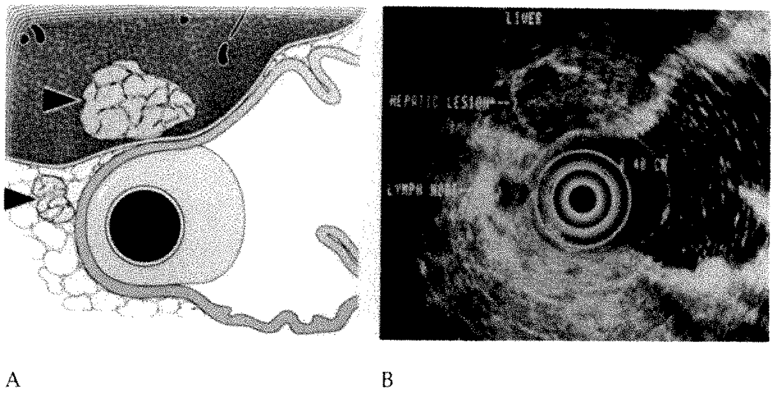

Fig 2. (A) The hepatic metastasis (upper arrow) *has increased in size after two courses of chemotherapy. A regional lymph node metastasis* (lower arrow) *has developed. (B) The hepatic metastasis* (upper arrow) *was shown to have increased in size by esophageal ultrasound. The regional lymph node metastasis* (lower arrow) *was seen by esophageal ultrasound.*

The chemotherapy induction regimen was a modified version of the etoposide, doxorubicin hydrochloride, cisplatin combination used by Wilke and colleagues [15]. Two courses of chemotherapy were planned: etoposide, 120 mg/m^2 on days 1, 2, and 3; doxorubicin, 20 mg/m^2 on day 1; and cisplatin, 100 mg/m^2 on day 2. The cisplatin administration necessitated hospitalization and was accompanied by vigorous intravenous hydration and diuresis induced by furosemide and mannitol. Aggressive antiemetic management including metoclopramide and dexamethasone was provided for all patients. The chemotherapy was repeated in 4 weeks for all patients except 1, who experienced sufficient toxicity that only a single chemotherapy course was given.

No dosage modifications for myelosuppression were made because only two courses of chemotherapy were planned. The second course of chemotherapy could be delayed for 1 week to allow for full hematological recovery, and the cisplatin dose could be reduced or deleted if any persistent renal functional impairment or hearing loss developed. All patients were followed closely during their induction chemotherapy in an effort to detect and manage any treatment-induced toxicities.

Four weeks after the final chemotherapy, patients underwent clinical assessment of symptomatic improvement, restaging esophagogastroduodenoscopy and EUS, chest radiography, and blood chemistry studies. Computed tomography and other staging procedures were repeated only if clinically indicated. After chemotherapy, an appraisal of tumor response based on symptom assessment, gross endoscopic appearance, and an EUS-determined clinical stage was assigned to each patient at the time of this reevaluation.

If there was no evidence of distant metastatic disease or unresectability, the patient underwent surgical intervention. Two patients were found to have distant metastatic disease at exploratory laparotomy and thoracotomy. They did not undergo resection. However, there was adequate tissue sampling to determine the pathological stage of the disease in 1 of these patients. The remaining 11 patients underwent a left thoracoabdominal incision for resection of the primary tumor and lymphadenectomy. In 6 patients, a left neck incision placed obliquely along the border of the left sternocleidomastoid muscle was used to complete the esophagectomy and allow reconstruction. A total gastrectomy and distal esophagectomy was required in 1 patient.

Examination of the resected esophagus and periesophageal tissue was performed, and a pathological stage was assigned. Clinical stage before and after chemotherapy, gross tumor response, and symptomatic response were then compared and correlated with the pathological stage.

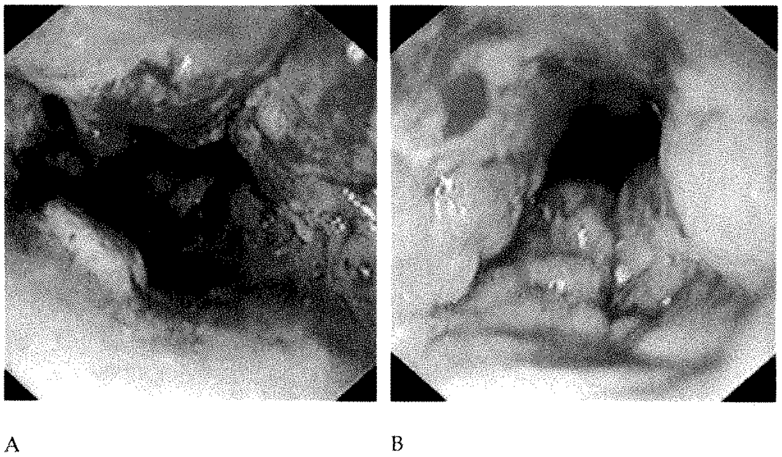

Fig 3. (A) Esophagoscopy of an esophageal carcinoma before chemotherapy. The bulky tumor nearly obstructed the lumen, but the esophageal ultrasound probe could be passed through the tumor. (B) After two courses of chemotherapy, there was a reduction of tumor bulk (partial response).

Table 1. Clinical and Pathological Stages of Esophageal Carcinoma

	Clinical											
	Pretreatment				Posttreatment				Pathological			
Patient No.	T	N	M	Stage	T	N	M	Stage	T	N	M	Stage
1	3	1	1	IV	3	1	1	IV	3	1	1	IV
2	3	0	0	IIa	3	1	0	III	3	1	0	III
3	3	1	0	III	2	0	0	IIa	3	1	0	III
4	3	0	0	IIa	3	0	0	IIa	2	0	0	IIa
5	3	1	0	III	3	1	0	III	3	1	0	III
6	2	0	0	IIa	2	0	0	IIa	2	1	0	IIb
7	3	1	0	III	3	1	0	III	3	1	0	III
8	3	1	0	III	3	1	0	III	3	1	0	III
9	3	1	0	III	3	1	0	III	3	1	1	IV
10	2	0	0	IIa	2	0	0	IIa	2	1	0	IIb
11	3	0	0	IIa	3	1	0	III	3	1	0	III

Results

Two patients (15%) did not complete the study. One of them was found to have a solitary hepatic metastasis in the left lateral segment of the liver (Figs 1, 2). This metastasis was not seen by any imaging modality except EUS, and its presence was confirmed by exploratory laparotomy and biopsy. The other patient did not have pretreatment staging because of the inability to pass the ultrasound endoscope through the malignant esophageal stricture. Although this patient was excluded from the study, it was possible to stage the tumor by EUS after the completion of two courses of chemotherapy.

Eleven patients (85%) completed the study. Nine (82%) patients, 8 with dysphagia and 1 with odynophagia, had reduction or relief of the preoperative symptoms. The tumor mass was reduced at endoscopy in 9 patients (82%), with one complete response (CR) and eight partial responses (PRs) (Fig 3). The pretreatment and posttreatment clinical stages and the pathological stages of the 11 patients are shown in Table 1.

Depth of tumor invasion (T) was correctly predicted in 9 of 11 patients by EUS, an 82% accuracy rate. One patient was understaged, and 1 patient was overstaged, each by one level. The predictive power of T3 by EUS was 88% (7/8); the predictive power of T2 by EUS was 67% (2/3). In all but 1 patient, EUS demonstrated no reduction in T after chemotherapy. The one EUS study that predicted reduction was the result of understaging in the posttreatment evaluation, as the T status remained unchanged from pretreatment to resection.

Regional lymph node status (N) was correctly predicted in 8 of 11 patients by EUS, a 73% accuracy rate. There were three incorrect clinical assessments of N; all were false-negative. The sensitivity for N was 70% and the specificity, 100%; the positive predictive value was 100% and the negative predictive value, 25%. In 1 patient, a reduction of N predicted by EUS was not seen in the pathological review of the resected specimen. In 2 patients (18%), N progression predicted by EUS was confirmed by pathological evaluation (Figs 4, 5).

There were three instances of metastases to distant sites among the 13 patients, one each to lung, liver, and celiac lymph nodes. Esophageal ultrasound detected the metastasis in the liver and celiac lymph nodes because these sites were in direct contact with the stomach during the examination. This technique could not detect the pulmonary metastasis because of the intervening air-filled lung, which did not allow an acceptable acoustic interface between the esophagus and the metastasis.

The stage of disease was correctly identified in 7 (64%) of 11 patients by EUS. All errors were the result of understaging, three by one stage (two stage IIb tumors misinterpreted as stage IIa tumors and one stage IV tumor misinterpreted as a stage III tumor) and one by two stages (a stage III tumor misinterpreted as a stage IIa tumor). One of the errors was the result of the inability of EUS to detect the pulmonary metastasis. The other three errors were due to EUS misinterpretation of N. In 1 patient, the combination of an understaging of T by one level and the false-negative interpretation of N resulted in the understaging of the tumor by two levels. The other incorrect determination of T did not affect the overall stage, as there were no regional lymph node metastases, and the stage remained IIa.

Comment

The prediction of pathological stage by clinical assessment is crucial if the effectiveness of preoperative chemotherapy in the treatment of esophageal carcinoma is to be

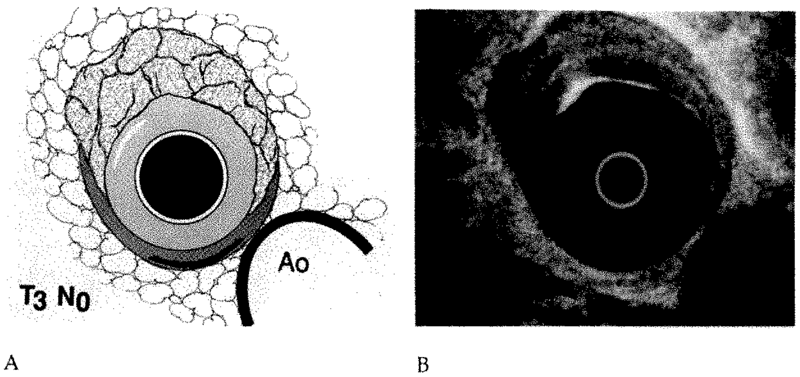

Fig 4. (A) A T3 N0 tumor before chemotherapy. (B) The T3 N0 tumor as seen by esophageal ultrasound. (Ao = aorta.)

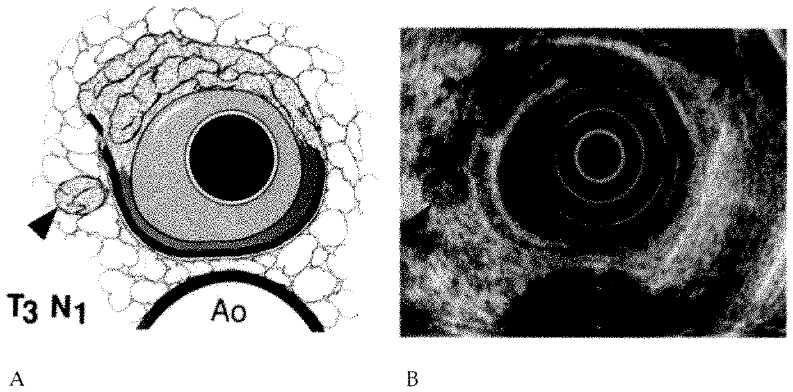

Fig 5. (A) The T3 N0 tumor in Figure 4 after two courses of chemotherapy. A regional lymph node metastasis (arrow) *has developed, and the tumor is now T3 N1. (B) The progression of the tumor to T3 N1 was documented by esophageal ultrasound, and the regional lymph node metastasis* (arrow) *was visualized.* (Ao = *aorta.)*

evaluated. Conventional staging tools such as esophagoscopy and barium esophagram demonstrate only the intraluminal extent of disease. Computed tomography of the chest is relatively insensitive for clinical staging of esophageal carcinoma except for extensive local disease and distant metastases. Assessment of symptoms is subjective and of limited value in the determination of clinical stage. None of these conventionally employed staging methods is adequate in the assessment of either the depth of esophageal wall invasion (T) or the presence of regional lymph node involvement (N). It is now known that these measures of malignant disease are of great prognostic importance in esophageal and gastrointestinal malignancies [1, 8, 9].

In 1983, the AJCC proposed that a clinical stage be defined according to the length of intraluminal esophageal tumor, the percentage of luminal obstruction, and the presence of palpable (cervical and supraclavicular) lymph nodes. This clinical staging system proved to be of limited value. The 1988 AJCC revision now recognizes only a pathological staging system based on the depth of esophageal wall invasion (T) and the presence of regional lymph node (N) and distant (M) metastases. Therefore, any approach to clinical staging must address these same variables. This necessitates the development of noninvasive clinical staging techniques that offer a fair prediction of pathological stage. The availability of such methods would aid in the selection of treatment modalities, allow study of these modalities, and afford accurate prognostication. With the increasing use of preoperative therapy, either induction chemotherapy or neoadjuvant chemotherapy and radiation therapy, the need for such a clinical staging method has increased.

Induction chemotherapy studies have failed to accurately assess the effects of preoperative chemotherapy and to correlate a clinical response with surgical findings. Forastiere and co-workers [4] reported a 47% response rate (1 complete response [CR] and 15 partial responses [PRs]) with cisplatin, vinblastine, and mitoguazone induction chemotherapy. The response rate was defined by reduction of tumor length as determined by barium esophagram. One CR was confirmed at operation. For patients with a PR, the only correlation to the surgical findings was that posttreatment tumor lengths were within 1 cm of measured tumor lengths at resection in 80% of patients.

Kies and associates [5] reported a response rate of 42% (3 CRs and 8 PRs) in patients treated with cisplatin and 5-fluorouracil. A CR was defined as elimination of dysphagia with no evidence of tumor by esophagoscopy or esophagogram. A PR was defined as reduction of dysphagia and reduction of tumor size by esophagoscopy, esophagram, or CT. The difficulty in determining a PR by standard means was noted. In addition, the staging after induction chemotherapy failed to detect mediastinal or abdominal metastases in 9 of 14 patients having operation. Residual tumor was found in all resected specimens. There was no further correlation or validation of the clinical responses with the pathological findings.

Hilgenberg and colleagues [6] had a response rate of 57% (13 CRs and 7 PRs) in patients treated preoperatively with cisplatin and 5-fluorouracil. A response was defined as symptomatic relief and reduction of tumor size by CT, barium esophagram, or esophagoscopy. There was one pathologically confirmed CR, and no further correlation between response to chemotherapy and surgical findings.

Ajani and co-workers [7] obtained a response rate of 49% (six CRs and 11 PRs) in patients receiving etoposide, 5-fluorouracil, and cisplatin induction chemotherapy. Responses were based on barium swallow, endoscopy with biopsy or cytology brushings, and CT. A patient with normalization of all studies and negative endoscopic biopsy specimens or cytological results was considered to have a CR. A marked reduction in tumor bulk was defined as a PR. On review of the resected specimen, there was only one CR. There was no further correlation between the clinical response and the stage.

In this study, there was an exceedingly high response rate (82%) of esophageal carcinoma treated with induction chemotherapy when assessed by symptom relief or endoscopy. These findings were not confirmed by EUS or pathologically determined stage. These results indicate that tumor size and symptom control are poor indicators of clinical stage. The AJCC recommends the variables of the TNM system as being the most important factors in the assessment of esophageal carcinoma. All tumors should, therefore, be assessed according to the TNM system. Currently, EUS is the most accurate method for clinical TNM staging. Esophageal ultrasound accurately predicts depth of tumor invasion (T) and regional lymph node status (N) and is superior to symptomatic or endoscopic assessment of the response of esophageal carcinoma to preoperative chemotherapy.

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DISCUSSION

DR HARVEY I. PASS (Bethesda, MD): When we are using computed tomograms for staging, size does not mean anything. Showing the consistency of a lymph node that is the same as the consistency of the esophageal cancer also really does not mean too much. How do you think endoesophageal ultrasound in the future is going to make an even bigger impact, possibly with other studies, to help with a histological diagnosis? Are we content to stop here, or do we have to be more invasive on the preoperative assessment as we have been with lung cancer?

DR RICE: Esophageal ultrasound is in its infancy. Currently we are familiarizing ourselves with the technique and the interpretation of the scans, and we are learning the power of esophageal ultrasound. What it has shown us to date is that the methods we have used in the past to assess the response to preoperative chemotherapy have been inadequate. We must realistically consider what we are subjecting our patients to. Preoperative chemotherapy and radiation therapy probably have not had an impact on survival of patients with esophageal carcinoma. We may learn this on completion of a phase III study, but at present, with the prediction of esophageal ultrasound, we can say that preoperative chemotherapy, at least the protocol used in the study, was totally ineffective. There is no need to wait until the survival data are complete. I think esophageal ultrasound will be crucial in the preoperative staging of patients with esophageal carcinoma. In the future, esophageal ultrasound may help direct therapy. I think it will be of utmost importance in the assessment of the effects of preoperative therapy.

Implantation of Cardioverter Defibrillators in the Post-Sternotomy Patient

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In an attempt to minimize the hazards of redo sternotomy or thoracotomy in patients who have undergone previous cardiac procedures, a technique has been developed for cardioverter defibrillator implantation that involves dissection through a left subcostal incision and placement of extrapericardial defibrillation patches. This approach was used in 22 consecutive patients who required an implantable cardioverter defibrillator 4 to 156 months after previous median sternotomy. Defibrillation threshold energy was less than or equal to 20 J in every patient. Ninety-one percent of patients were extubated during the first 24 hours and were transferred out of the intensive care unit by the second postoperative day. One patient died of an acute myocardial infarction 3 days postoperatively (1/22, 4.5%). It was necessary to replace one lead for mechanical failure of an adapter, one patch required repositioning, and 1 patient needed drainage of a persistent pleural effusion (3/22, 13.6%). No further complications occurred during 3 to 27 months of follow-up. Advantages of the subcostal approach included prompt extubation, a single incision, and minimal morbidity. This approach is safe and effective, and is the method of choice for implantation of a cardioverter defibrillator in patients who have undergone prior sternotomy.

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The precise role of the implantable cardioverter defibrillator (ICD) in the nonpharmacological treatment of sudden cardiac death and malignant ventricular arrhythmias continues to evolve as clinical experience expands and device technology becomes more sophisticated. As implantations of the device become more frequent, a number of refinements in surgical technique have been reported [1, 2]. The surgical approaches for primary ICD insertion include median sternotomy [3–5], left thoracotomy [6–8], and subxiphoid [9] or subcostal [10, 11] techniques. Patients who have undergone previous open heart operations, particularly those with patent aortocoronary bypass grafts, present the surgeon with additional technical difficulties with conventional implantation techniques because of the presence of postoperative adhesions and the potential risks of graft, cardiac, or great vessel injury.

To minimize the hazards of standard redo sternotomy or thoracotomy in patients who have undergone previous cardiac procedures, a technique for placement of an ICD has been developed that involves dissection through a left subcostal incision and use of extrapericardial defibrillation patches. This report describes the operative technique and the results of its application in 22 consecutive patients undergoing implantation of the device after previous median sternotomy.

Material and Methods

Patient Population

During the 26-month period from July 1989 to September 1991, 128 automatic cardioverter defibrillators were implanted at the Medical College of Virginia and McGuire Veterans Administration Hospitals, Richmond, VA, by one attending surgeon (R.J.D.). Twenty-two (17%) of these devices were implanted after previous median sternotomy, and these patients form the basis of this report. All data are expressed as the mean ± the standard error of the mean.

The duration between the previous cardiac procedure and ICD placement ranged between 4 and 156 months with a mean of 52 ± 9 months. The majority of the patients were men (21/22); the mean age was 62 ± 7 years (range, 44 to 77 years). All patients except 2 had ischemic heart disease, and of these 20, 18 (90%) had ejection fractions equal to or less than 0.30. Overall mean ejection fraction was 0.27 ± 0.02. Seventeen patients had undergone previous coronary artery bypass grafting, 4 of whom had had two previous coronary revascularization procedures. The left internal mammary artery had been used in 2 of these patients. Four patients had undergone combined coronary artery bypass and valve replacement procedures. Two patients without coronary artery disease had had valve replacement for rheumatic valvular disease.

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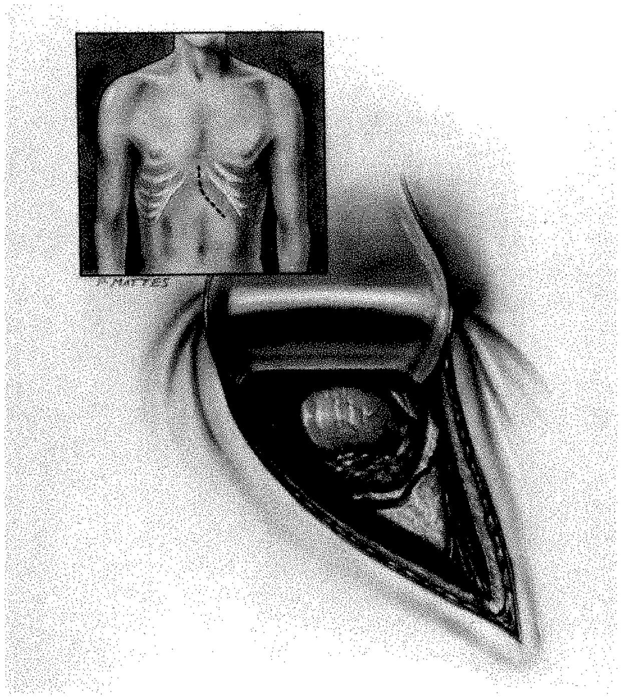

Fig 1. The left subcostal incision is performed as depicted in the inset. The diaphragm and pericardium are exposed by upward retraction of the costal margin.

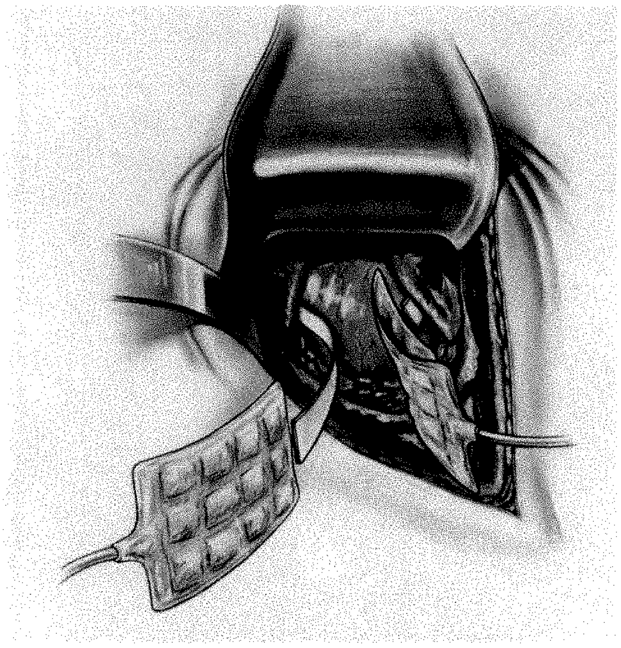

Fig 2. Defibrillation patch electrodes are positioned extrapericardially along both lateral margins of the heart.

The most common indication for use of the ICD was the presence of ventricular tachycardia that remained inducible despite drug therapy (20/22 patients, 91%). Two patients were seen following a documented clinical episode of ventricular fibrillation and had noninducible arrhythmias in the electrophysiological laboratory.

Operative Technique

All patients received a first-generation cephalosporin intravenously on call to the operating room. They were positioned supine on a fluoroscopy table with external defibrillation patches and electrocardiographic leads in place. Cardiopulmonary bypass was available, and a perfusionist was on standby. General orotracheal anesthesia was employed. A high-dose narcotic, muscle-relaxant anesthesia technique was used. Central venous access and invasive monitoring were used in all patients. The skin preparation involved the chest, abdomen, and both groins. The chest was prepared laterally to the table level to allow for pleural tube placement when needed.

The left subcostal skin incision was begun at the xiphoid process and carried one to two fingerbreadths below and parallel to the costal margin (Fig 1). The anterior rectus fascia and muscle were divided at this level using electrocautery to achieve hemostasis. A pocket was created beneath the rectus muscle inferiorly and laterally and packed with a sponge soaked in antibiotic solution. Cephalad retraction of the left costal margin using an upper-hand retractor or ring-type self-retaining retractor was necessary to expose the plane of dissection underlying the xiphoid process. The dissection was carried through the diaphragm at and to the left of the midline under direct vision with the use of a fiberoptic headlight. The costal attachments of the diaphragm were either bluntly separated or sharply divided. The anterior mediastinum was exposed, and the diaphragmatic surface of the right ventricle or the overlying pericardium, when present, was identified. The dissection was continued anteriorly and laterally in the extrapericardial space. The areas between the pericardium and the right and left pleura were carefully dissected. An area large enough to accommodate the surgeon's hand was necessary to place the flattened defibrillator patches along the extrapericardial borders of the heart (Fig 2).

The defibrillation patches were placed such that the cathode lay over the lateral left ventricular pericardium and the anode over the lateral wall of the right atrium and ventricle. Silk ligatures were used to fix the defibrillation patches to the pericardium, even though surrounding adhesions often confined the patches securely between the lungs and pericardium.

In our initial experience, epicardial screw-in electrodes were positioned after dissection of a small area of the diaphragmatic surface of the right ventricle. Although this surface was often relatively free from adhesions, care was taken to avoid injury to the ventricle or bypass grafts. Bipolar epicardial screw-in leads were placed approximately 1 cm apart into a nonscarred area of exposed myocardium.

To avoid unnecessary dissection around the heart and the possibility of ventricular laceration or graft injury in these patients with a previous sternotomy, transvenous pacing and sensing electrodes became preferred to epicardial leads. A transverse left subclavicular incision 1 to

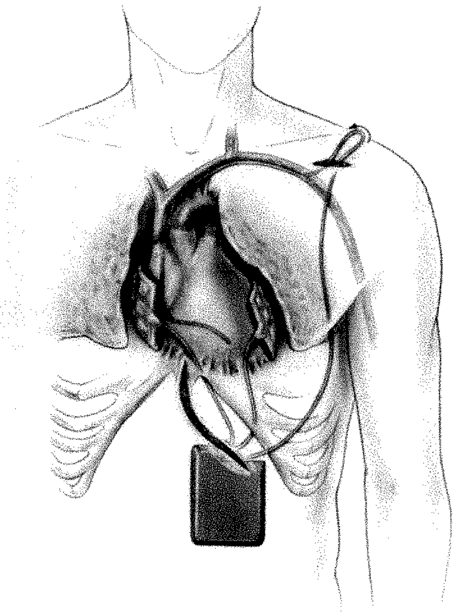

Fig 3. The completed procedure with a transvenous endocardial lead tunneled down to the subcostal incision and the generator implanted beneath the rectus muscle. The patches are positioned between the pericardium and the pleura.

2 cm long was performed. A 100-cm bipolar endocardial lead was inserted into the left subclavian vein using the Seldinger technique. The lead was positioned fluoroscopically in the right ventricular apex, and routine pacing and sensing variables were examined. Both active and passive fixation leads were employed. Active fixation leads were favored (9/10 patients) because of our concern regarding dislodgment of tined leads during defibrillation testing. The lead was securely fixed to the pectoralis fascia with a nonabsorbable ligature to eliminate the possibility of migration. The lead then was tunneled through the subcutaneous tissue to the subrectus generator pocket (Fig 3).

Defibrillation threshold testing was performed using a standardized protocol. Testing was begun at 20 J, and shock energy was decreased until the defibrillation threshold was defined. Warm saline solution was instilled into the chest, and all metal retractors were removed before shock delivery. Defibrillation was performed at full lung inflation to maximize contact of the patches with the pericardium. At least 2 minutes were allowed for hemodynamic stabilization between each test. Defibrillation patch configuration was considered acceptable only if three consecutive defibrillations were successful at less than or equal to 20 J.

The defibrillator generator was then connected, interrogated, activated, and tested. If bleeding at the epicardial surface of the right ventricle had occurred, a soft closed-suction mediastinal drain was left in place; otherwise no drain was used. The ICD was deactivated and placed beneath the rectus muscle. Meticulous hemostasis was obtained after generous irrigation with antibiotic-containing saline solution. If either hemithorax had been entered, a pleural tube was used for drainage. The diaphragm was reapproximated to the costal margin. The anterior rectus fascia was closed with a continuous nonabsorbable suture, and this was followed by closure of the subcutaneous tissue and skin. Fluoroscopy was used to confirm proper patch position and verify satisfactory placement of the endocardial lead in the right ventricular apex before the patient left the operating room.

Postoperatively antiarrhythmic medications were restarted on an individual basis. Antibiotic administration was continued for 24 hours or until the pleural tubes were removed. Extubation was often performed in the operating room but was delayed when there had been prolonged defibrillation testing or when the patient had not completely metabolized the anesthetic agents. Postoperative pain was treated with epidural narcotics, supplemented intravenously as needed. The ICD was activated immediately after completion of the procedure. The patients were monitored in an intensive care unit for at least 24 hours.

The patients then were transferred to the ward and had telemetry monitoring and resumption of activity as tolerated. Before discharge, ICD testing in the electrophysiological laboratory was performed in every patient on the fifth to seventh postoperative day.

Patients were examined by the operating surgeon in the clinic 2 and 6 weeks after hospital discharge. Subsequent routine examinations were performed by the electrophysiologists.

Results

Operative Results

Adequate defibrillation energy thresholds were obtained in each patient. Mean defibrillation energy was 16 ± 5 J (range, 7 to 20 J). The most commonly employed configuration was a large patch on the left lateral border of the pericardium as the cathode and an anodal patch in the right lateral position (19 patients). In 3 patients, lateral positioning was not successful, and patches were placed in extrapericardial anterior and posterior positions to achieve adequate thresholds. Standard ICD devices were implanted in most patients (CPI Ventak model 1550 [Cardiac Pacemakers, Inc, St. Paul, MN], 9 patients; CPI Ventak model 1600, 2). A high-output ICD (CPI Ventak model 1555) was implanted in 1 patient with ventricular fibrillation at electrophysiological study and a defibrillation threshold of 20 J. Epicardial screw-in rate-sensing leads were placed on the diaphragmatic surface of the right ventricle in 12 patients. Transvenous endocardial leads were placed in 10 patients and became our preferred lead for patients receiving devices with antitachycardia pacing (Telectronics model 4210 [Telectronics Pacing Systems, Inc, Englewood, CO], 8 patients) or bradycardia support (Telectronics model 4203, 2 patients). R-wave amplitude ranged from 6 to 35 mV (mean amplitude, 17 ± 2 mV). Pacing threshold at a pulse width of 0.5 ms ranged between 0.5 and 1.9 V (mean threshold, 0.9 ± 0.2 V).

These variables were not significantly different between endocardial and epicardial leads.

Only 6 of the 22 patients had the pericardium closed at the time of the initial procedure. There was no appreciable difference in the difficulty of the dissection between patients who had previously open and those with previously closed pericardiums. There were no instances of intraoperative damage to bypass grafts, and no patient required a sternotomy or thoracotomy.

Early Postoperative Results

Most of the patients (13/22, 59%) were extubated on the evening of ICD insertion and nearly all (20/22, 91%), by the first postoperative day. These 20 patients were all transferred out of the intensive care unit within the following 24 hours. Atrial tachyarrhythmias prevented transfer and ICD activation until the third postoperative day in 1 patient, and repeated episodes of ventricular tachycardia in another delayed transfer until the fifth postoperative day. Extubation was delayed until the third day in 1 patient who received excessive fluid and was treated for pulmonary edema. Chest tube drainage was minimal (mean amount, 200 ± 58 mL; range, 0 to 900 mL), with tube removal by the first postoperative day in all but 2 patients. Bilateral drainage tubes were necessary in 7 patients, and single tubes in 13 patients. No chest tubes were required in 2 patients.

Although left basilar atelectasis was common, clinical pneumonia or critically impaired ventilatory function was not seen after use of the subcostal approach. One patient required readmission for drainage of a symptomatic left pleural effusion 3 weeks after cardioverter defibrillator implantation.

Two patients had to be returned to the operating room. One ICD was revised on the fifth postoperative day for oversensing related to a mechanical lead problem involving a fractured adapter. Buckling of a defibrillation patch was noted on a predischarge chest roentgenogram in 1 patient, and the patch was repositioned on postoperative day 10. There was 1 perioperative death (1/22, 4.5%). It occurred 3 days after ICD placement and was related to an acute anterior myocardial infarction. This patient had undergone combined five-vessel coronary artery bypass grafting and mitral valve replacement 4 months earlier. Postmortem examination demonstrated occlusion of two grafts and an acute infarction. There were no other complications in this group of patients.

Formal electrophysiological testing was conducted before discharge and confirmed ICD function in each patient. Most patients (16/22, 73%) were either discharged home or transferred for further medical workup by the tenth postoperative day (range of hospital stay, 6 to 23 days).

Late Postoperative Results

Patients have been followed for intervals of 3 to 27 months after hospital discharge. No patient has been lost to follow-up. During this period there has been only 1 death. It was due to a documented noncardiac cause and was not an arrhythmia-related death.

Comment

It is estimated that more than 24,000 patients have received ICDs to date, and it can be assumed that with further technological advances, the number of implantations will continue to increase dramatically [12]. As implantation of the device becomes more commonplace, more patients will be seen who have undergone prior cardiothoracic procedures.

Early techniques for implantation of the cardioverter defibrillator emphasized the need to obtain generous operative exposure in an expeditious and safe matter [7]. The left anterior thoracotomy approach was the most commonly employed technique [2, 6–8, 13]. Many centers even preferred a median sternotomy for primary implantation [3–5].

However, as experience increased, some surgeons became convinced that more limited approaches carried a lower morbidity and mortality. Watkins and associates [9] introduced the subxiphoid approach in 1982. This approach obviated the need for thoracotomy or sternotomy but employed two separate incisions: a subxiphoid incision to place intrapericardial patches and epicardial wires and a second incision for the generator pocket. Excellent results were obtained with this more limited approach [14]. The subcostal thoracotomy, introduced by Parsonnet and colleagues [15] in 1965, was initially used for pacemaker electrode insertion. Lawrie and associates [10, 16] first used the subcostal approach for ICD placement in 1984. This approach employed only a single incision for patch and generator placement and has been used with excellent results for primary ICD insertion.

Patients who have undergone prior sternotomies for cardiac procedures represent an additional technical challenge because of the presence of postoperative adhesions and the potential risks of bypass graft, cardiac, or great vessel injury. Although the left thoracotomy approach has been endorsed for patients with prior sternotomy [7, 17], this technique has several disadvantages. It results in a painful, cosmetically unattractive incision, can be difficult in patients with prior internal mammary artery grafts, and requires a separate incision for generator implantation. A redo median sternotomy also carries potential hazards [18, 19]. Lytle and colleagues [19] demonstrated that the risk of redo sternotomy, especially in the presence of patent internal mammary grafts, is appreciable.

The subcostal approach has several advantages in a patient with a prior sternotomy. Patch placement can be performed in either anterior-posterior or lateral-lateral extrapericardial locations through a single, cosmetically superior incision. Postoperative adhesions from previous procedures can be avoided, thus minimizing the potential risks of graft, cardiac, or great vessel injury. Either transvenous endocardial or epicardial pacing or sensing leads can be easily placed. There were no serious problems with bleeding or graft injury with epicardial lead placement using this approach, although as our experience increased, the endocardial pacing or sensing lead was favored because it eliminated the need for dissection inside the pericardium. In all instances, an adequate defibrillation configuration could be achieved with this approach in our 22 consecutive patients.

The operative mortality of ICD placement as a primary procedure ranges from 1.2% to 4.5% in collected large series [20–29]. Patients with depressed left ventricular function have been shown to have an increased mortality rate. Kim and associates [30] reported an early mortality rate of 11% in patients with a left ventricular ejection fraction of less than 0.30 compared with 0% in those with preserved ventricular function. Other studies [31, 32] examined patient subsets with depressed left ventricular function and found a similar pattern. There was only 1 death in our series, and it was secondary to an acute myocardial infarction. Although the series is small, this is considered an acceptable result in this high-risk group of patients, all of whom had undergone prior cardiac procedures and 81% of whom had ejection fractions less than or equal to 0.30.

The reported incidence of early complications after primary ICD insertion by median sternotomy or thoracotomy ranges from 6% to 30% [20–29]. Some groups [9, 10, 14] showed a substantial decrease in complication rates for the less invasive subcostal or subxiphoid approaches for primary ICD insertion. This report confirms these findings in a high-risk population of patients who have undergone previous sternotomy. The early complication rate in this series was low (3/22, 13.6%), and there were no instances of infection, erosion, or bleeding.

The subcostal approach also resulted in a very low incidence of pulmonary complications in these patients (1/22, 4.5%). In a previous report [25], 29% of patients had pulmonary complications after ICD placement. In the present series, the single pulmonary complication was a minor one involving a persistent pleural effusion.

In summary, this series supports the utility and advantage of the subcostal approach for ICD insertion in patients who have undergone a previous sternotomy. The less invasive subcostal approach avoids adhesions and the potential risks of graft, cardiac, or great vessel injury. The difficulties associated with redo sternotomy or thoracotomy are avoided. With appropriate retraction, subcostal exposure yielded satisfactory flexibility for defibrillation patch placement. There was minimal morbidity in this high-risk group of patients, allowing prompt extubation and ambulation. The subcostal approach is considered to be a safe and effective technique and is our method of choice for ICD insertion in patients with a previous sternotomy.

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DISCUSSION

DR JOHN M. KRATZ (Charleston, SC): We have not tried this approach but may try it as a new procedure before doing it on a post-sternotomy patient. In some of the patients we operate on in this situation, the pericardium is closed; in some, it is partially open; and in some, wide open. During your presentation, I was trying to imagine a patient with a pericardium wide open. Sometimes we do not know because the patient was operated on elsewhere some time ago. Does that affect the efficacy of this approach, or can you find yourself actually not looking at the pericardium but at the heart while you are dissecting a widely opened pericardium?

DR DAMIANO: I think that is an excellent question. In most of the patients, it is fairly easy to identify at least one of the borders of the pericardium because you are coming up from below and through the diaphragm. It is fairly evident that after you divide the diaphragmatic muscle, you are usually on the pericardial surface of the heart. It is important to perform the dissection right under the xiphoid process. I am sure you have had a lot of experience with redo coronary bypass procedures, and there usually is a space overlying the diaphragmatic surface of the right ventricle, even if the pericardium has been left widely open. I think it is important to carefully identify when you go through the diaphragm. If you do not see the pericardium, you know you need to carry your dissection in an anterolateral direction. The key to this approach is both staying anterior, hugging the costal margin, and moving laterally as quickly as possible after you divide the diaphragm. This does not present a very difficult clinical problem. I think the advantage of this approach, certainly with the use of transvenous endocardial leads, is that there is no requirement for any dissection around the heart and no chance of injuring the vein or internal mammary grafts.

DR LYNN H. HARRISON (New Orleans, LA): That was a very nice presentation. These patients were very sick, as they always are, and you got them through splendidly. I do have a couple of points to raise.

It seems to me that one of your premises is that these patients were able to be separated from the ventilator sooner by virtue of this technique, yet a substantial percentage of them were intubated, I gather, overnight. In addition, division of the rectus as well as a portion of the diaphragm represents a lot of muscle cutting. If an anterior thoracotomy is used with a muscle-splitting procedure, it seems that we do not cut quite that much muscle, and postoperative pain with the anterior incision has not been an unwieldly problem.

Finally, I noticed you had one problem with a lead fracture. With the technique that you described, as I understand it, you are tunneling that lead subcutaneously, passing it over the costal margin, which is one of the techniques that is associated with a lead-fracturing problem. Would you comment on that?

DR DAMIANO: Those are excellent points. I am not sure whether this technique really offers a substantially earlier extubation compared with standard techniques, and I really did not mean to imply it. About 70% of our patients were extubated immediately after the operation. I think the biggest single limiting factor in early extubation of these patients is a lack of cooperation between the surgeon and the anesthesiologist.

I would like to emphasize that epidural narcotics are important in terms of limiting the immediate postoperative pain. Having had experience with both the thoracotomy and the subcostal incision, I think the latter is a little bit less invasive and less painful, though, as you point out, there is pain with this incision. However, I do not think there is much pain from the splitting of the costal attachments of the diaphragm. Those of you who have used this approach know that usually that can be done very easily, almost with a finger, and we are not talking about a very thick muscular attachment. There is some pain in dividing the rectus muscle. In some patients, we have actually been able to separate the rectus muscle and slip the device in, and I think with some of the newer device designs this will probably become the norm rather than the exception. These defibrillators are bulky, and their rectangular design does not lend itself to being squeezed between the muscle fibers of the rectus. Some of the newer defibrillators have oval shapes that are much easier to insert. Another advantage of the subcostal approach is that it requires only one incision. Certainly our patients seem to be a lot happier with a single incision in a cosmetically acceptable place than with a thoracotomy scar and a separate subcostal incision required for a standard implantation.

I think that with the advent of nonthoracotomy systems, things may be changing. In many of the post-sternotomy patients, a nonthoracotomy approach presents a very viable option. Since we prepared this presentation, we have performed nonthoracotomy implantation in 2 patients with excellent results.

Time to First Pulse After Automatic Implantable Cardioverter Defibrillator Implantation

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Should automatic implantable cardioverter defibrillator (AICD) power sources be explanted and discontinued if they have not pulsed during the first generator life? We have followed 59 patients an average of 23 months (range, 3 days to 8.4 years) after AICD implantation. The indication for AICD implantation was based on clinical dysrhythmia, history of sudden death, and findings at electrophysiologic study. Thirty-eight of 59 patients (64%) had experienced sudden death and 52/58 (90%) were inducible at electrophysiologic study. Excluding 5 inappropriate pulsing episodes, 31 of 59 patients (53%) had 235 pulses (range, 1 to 36; median, 2 pulses). The time to first pulse after implantation ranged from 1 day to 3.5 years with a median time of 2 months. In 6 patients, the first pulsing occurred later than 1 year after AICD implantation. Fifteen generators demonstrating impending power source failure have been replaced in 11 patients. Power source depletion occurred at an average of 24.1 months (range, 8 to 40 months). In 3 patients, the first pulsing occurred after generator depletion and replacement. By univariate analysis, none of 13 variables (sex, age, cardiac disease process, functional class, previous myocardial infarction, sudden death history, ejection fraction, type of dysrhythmia, inducibility with electrophysiologic testing, number of extra stimuli required for induction, left ventricular aneurysm resection, endocardial resection, or concomitant operation) was found to be a predictor of pulsing ($p > 0.05$). We conclude that the majority of patients with pulses after AICD implantation will have them during the first 6 months. However, in this group of patients at high risk for sudden death by ventricular dysrhythmia, absence of pulsing during the first battery life does not justify explantation and discontinuance of AICD back-up.

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Sudden cardiac death is the leading cause of death in the United States [1, 2]. Extensive research has sought to determine those patients at risk for sudden cardiac death with the goal of prevention by pharmacologic and surgical modalities [3–7]. The first totally implantable, automatic cardiac defibrillator was successfully tested in dogs at the University of Missouri in 1970 by Dr John Schuder and colleagues [8]. Pioneering research and subsequent introduction of a clinical model by Dr Michel Mirowski and colleagues added a third treatment option to be considered in addition to surgical and pharmacologic management of malignant ventricular dysrhythmia [9–11]. Thousands of these devices have now been implanted in patients worldwide, and their efficacy of eliminating death due to ventricular dysrhythmia, in appropriately selected patients, is increasingly accepted [12–16].

Since the initiation of our clinical program using the automatic implantable cardioverter defibrillator (AICD) in 1982, we have been convinced that the device has saved lives. However, we are increasingly confronted with the dilemma of what to do with patients in whom the AICD does not pulse during the first several years after implantation. The purpose of this report is to present a retrospective analysis of our patients undergoing implantation of an AICD in an effort to answer the research question: should AICD power sources be explanted and discontinued if they do not pulse during the first generator life?

Material and Methods

Patient Population

Between October 1982 and April 1991, 59 patients had implantation of complete AICD systems at the University of Missouri Health Sciences Center. The patient population consisted of 48 male and 11 female patients whose age ranged from 17 to 80 years with a mean age of 60 years. The underlying cardiac pathology was ischemic heart disease in 49 patients, cardiomyopathy in 9, and idiopathic in 1. The defibrillator model implanted was the Intec AID-B in 11 patients and Cardiac Pacemaker Inc models 1500 in 5 patients, 1510 in 2 patients, 1520 in 27, and 1550 in 29 patients.

Indications for AICD implantation included clinically observed malignant ventricular dysrhythmia in 58 patients (98%), a history of sudden death in 41 (69%), and inducible ventricular dysrhythmia in 52 of 58 patients tested (90%). All patients had failed or not tolerated pharmacological dysrhythmia suppression. Two patients had failed directed ablative endocardial resection, and the

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remaining patients were not suitable candidates for the procedure. Eighteen patients had concomitant operation at the time of AICD implantation. Ten patients had coronary artery bypass grafting, 7 patients had left ventricular aneurysm resection with or without coronary artery bypass grafting, and 1 patient had mitral valve replacement. Forty-one patients had isolated AICD implantation.

Surveillance After AICD Implantation

Patients were routinely seen as outpatients every 2 to 3 months if no pulsing occurred. When patients experienced single pulsing without associated symptomatology, they were admonished to immediately report the pulsing by a telephone call. Further interrogation at that time determined whether patients should be seen immediately or electively. When pulsing was associated with symptomatology or when multiple pulses occurred, patients were evaluated immediately.

Complete follow-up was achieved with the follow-up time ranging from 3 days (time of death) to 8.4 years with a mean follow-up period of 23 months.

Operational definitions of pulsing were divided into three categories: appropriate pulsing was used to describe those pulses preceded by dizziness or syncope, those documented by appropriate monitoring, or those that awakened patients from sleep. Questionable pulses were those pulses that were not preceded by symptoms and those in which the patient was unaware of a pulse with documentation being by device interrogation. Inappropriate pulses were defined as those with obvious extraneous interference and those where monitored rhythm strips documented inappropriate pulsing.

Automatic implantable cardioverter defibrillator pulse generators were replaced according to elective replacement indicators or at the time of recognized power source depletion.

Predictors of Pulsing

Thirteen potential predictors of pulsing including sex, age, cardiac disease process, functional class, previous myocardial infarction, sudden death history, ejection fraction, type of dysrhythmia, inducibility with electrophysiologic testing, number of extrastimuli required for induction, left ventricular aneurysm resection, endocardial resection, and concomitant operation were scrutinized for significance by appropriate statistical analyses.

Statistical Analyses

For ordinal and continuous variables the two groups were compared using a Wilcoxon rank sum test. For dichotomous variables, a Fisher's exact test was used to compare proportions. The remaining categorical variables were analyzed using χ^2 tests.

Results

Thirty-six of 59 patients (61%) experienced AICD pulsing during the follow-up period. For statistical analysis patients were grouped according to whether they experienced a pulse or not. Those with documented inappropriate pulsing (5 patients) were included in the "no pulse" group. Thirty-one of 59 patients (53%) met the criteria for appropriate (27 patients) or questionably appropriate (4 patients) pulsing. These 31 patients had a total of 235 pulses with a range of 1 to 36 pulses per patient (median, 2 pulses per patient). Of those in whom the AICD pulsed, the time to first pulse after implantation ranged from 1 day to 3.5 years with a median time of 2 months.

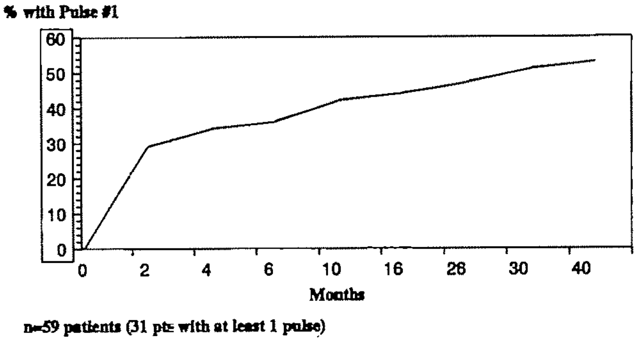

Fig 1. A continued incremental appearance of first pulsing is observed.

Of the 59 patients, 21 (36%) had a pulse during the first 6 months, 4 patients (6.8%) had a pulse between 6 months and 1 year after implantation, and 6 patients (10.2%) had an appropriate pulse for the first time at 1 year or greater after implantation.

Figure 1 shows graphically the time to first pulse in the 59 patients. Although the curve is steepest during the first 2 months, there is a continued incremental appearance of first pulsing during the follow-up period.

Figure 2 is a bar graph of the time to first pulse in 31 patients experiencing at least one pulse. Of those patients having pulsing during follow-up, 21 patients (68%) had a pulse during the first 6 months after AICD implantation. However, 4 patients were noted to have the first pulse 2 years or longer after AICD implantation.

Eleven patients required 15 generator replacements at 8 to 40 months after previous AICD implantation. The mean interval to AICD replacement was 24 months. In 3

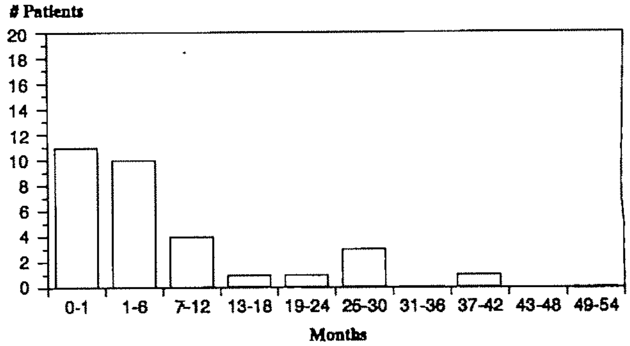

Fig 2. Time to first pulse in 31 patients experiencing appropriate pulsing.

Table 1. Potential Predictors of Automatic Implantable Cardioverter Defibrillator Pulsing

Variable	Pulse	No Pulse	p Value[a]
Sex	23M/8F	25M/3F	0.18
Mean age (y)	61 ± 9.3	60 ± 13.5	0.79
Cardiac disease			
Ischemic	25	24	0.40
Cardiomyopathy	6	3	
Idiopathic	0	1	
NYHA III or IV	11/23 (48%)	12/23 (52%)	0.62
Recent MI (<3 mo)	5/12 (42%)	7/12 (58%)	0.39
Sudden death	22/41 (54%)	19/41 (46%)	0.79
Ejection fraction <0.35	14/28 (50%)	14/28 (50%)	0.71
Ejection fraction	0.39 ± 0.15	0.37 ± 0.13	0.69
Clinical dysrhythmia			
Sustained VT	12 (57%)	9 (43%)	0.48
Nonsustained VT	5 (50%)	5 (50%)	
Ventricular fibrillation	14 (54%)	12 (46%)	
Inducible			
Yes	28/51 (55%)	23/51 (45%)	1.000
No	3/6 (50%)	3/6 (50%)	
Extrastimuli			
≤2	9/14 (64%)	5/14 (34%)	0.375
≥3	15/30 (50%)	15/30 (50%)	
Concomitant operation			
Yes	19/31 (61%)	12/31 (39%)	0.157
No	12/28 (43%)	16/28 (57%)	
LVA resection	3/7 (43%)	4/7 (57%)	0.698
Endocardial resection			
Yes	2/5 (40%)	3/5 (60%)	0.557
No	29/54 (54%)	25/54 (46%)	

[a] See statistical analysis section.

LVA = left ventricular aneurysm; MI = myocardial infarction; NYHA = New York Heart Association functional class; VT = ventricular tachycardia.

patients, the first pulsing occurred after initial generator depletion and replacement.

Thirteen potential predictors of pulsing were analyzed in an effort to define subpopulations at greater or lesser risk for pulsing after AICD implantation. As can be seen from Table 1, none of these potential predictors significantly predicted pulsing.

Comment

Should AICD power sources be explanted and discontinued if they have not pulsed during their first generator life? The answer to this question hinges on several factors, including how well we can select patients who predictably will have recurrent ventricular dysrhythmia, the frequency and temporal relationship of recurrent ventricular dysrhythmia, the ability to identify appropriate pulsing with the defibrillator, and to a lesser extent the battery life of the AICD pulse generator.

As only patients with observed or predictable malignant ventricular dysrhythmia, in spite of medical and surgical therapy, are chosen for AICD implantation, it is not surprising to observe that the majority experience pulsing. This observation has been made by others [13, 17, 18]. Because the patient selection process is based largely on the probability of future malignant ventricular dysrhythmia, we had hoped to identify a subpopulation within this high-risk group that might not require a continued commitment to AICD backup if pulsing did not occur during the battery life of the first power source. In contrast to the findings by Myerburg and colleagues [17], who observed no patient who had the first appropriate shock greater than 16 months after AICD implantation, 4 of our patients had the first pulse 2 years or longer after AICD implantation. Indeed, in 3 patients, the first pulsing occurred after initial generator depletion and replacement. (We have now observed a patient who pulsed appropriately for the first time at 60 months after AICD implantation, at which time the patient had received his third pulse generator.)

Others have also shown that malignant ventricular dysrhythmia and first pulse may occur remotely from the initial AICD implantation. Forgoros and colleagues [19] concluded that in their clinical experience, the cumulative risk of receiving an appropriate pulse was 33% ± 7% after 1 year, and this rose to 64% ± 10% at 4 years. In 14 of their patients who were followed for 24 months without receiving an appropriate shock, the actuarial risk of receiving an appropriate shock was 29% ± 14% during the next 24 months. The maximum amount of time to the first appropriate shock was 39.7 months in the series reported by Mercando and co-workers [14].

Battery depletion or elective replacement indicator charge time of the AICD prompted pulse generator replacement at an average of 24 ± 8.9 months in this series. The average time to failure of the 28 units removed for battery depletion in the series reported by Mercando and colleagues [14] was 19.8 ± 6.9 months. Although the elective replacement indicator may be overly conservative for patients who have not had a pulse [20], it remains clear that some patients will experience their first appropriate pulse after battery depletion and replacement.

We were unable to identify a subpopulation of patients in this high-risk group in which absence of pulsing could be predicted. Several possibilities for this exist including our small sample size, the retrospective nature of the review, and the inability to distinguish with absolute precision appropriate from inappropriate pulsing. This may, in part, also explain the conflicting reports in the literature regarding predictors of appropriate pulsing. Levine and colleagues [18], from a large cohort of patients, reported that ejection fraction less than 0.25 and the presence of congestive heart failure of New York Heart Association class III or IV were strong predictors of appropriate pulsing in patients receiving AICD. In contrast, Myerburg and co-workers [17] concluded that ejection fraction does not discriminate between those who will and will not have pulses after AICD implantation, though it did discriminate risk of death during follow-up. In the present series, left ventricular ejection fraction analyzed as a discrete or continuous variable did not predict pulsing. Patients in whom appropriate pulses occurred for the first time greater than 1 year after AICD implantation had left ventricular ejection fractions ranging from 0.15 to 0.70.

In the study by Levine and associates [18], the presenting ventricular dysrhythmia, electrophysiological findings, extent of coronary artery disease, and antidysrhythmic drug status at the time of hospital dismissal did not correlate with presence or time to first AICD pulsing. We were particularly intrigued that the ability to induce ventricular dysrhythmia in the electrophysiology laboratory did not predict pulsing in this high-risk group of patients, most of whom had demonstrated malignant ventricular dysrhythmia or sudden death before AICD implantation.

In conclusion, in our experience, the majority of patients who have a pulse after AICD implantation will have it during the first 6 months. In this high-risk group, we were unable to identify factors that predicted pulsing. Automatic implantable cardioverter defibrillator devices that record and store retrievable electrocardiographic activity before pulsing and further observation of larger patient populations will allow for more definitive risk stratification. This may allow identification of subpopulations that will not require life-long commitment to AICD backup. However, based on present highly selective indications for AICD implantation, absence of pulsing during the first battery life does not justify explantation and discontinuance of AICD backup.

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Pulmonary Embolism in the Cardiac Surgical Patient

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Pulmonary embolism (PE) is thought to occur infrequently after cardiac operations, possibly because systemic heparinization during cardiopulmonary bypass prevents deep vein thrombosis. This retrospective study was undertaken to determine the actual incidence of PE after cardiac operations and to identify risk factors. Between January 1, 1985, and December 31, 1989, 5,694 adult patients (>18 years old) had open heart operations at the Johns Hopkins Hospital. Thirty-two patients (20 men and 12 women) had PE within 60 days of operation, an overall PE incidence of 0.56%. The diagnosis of PE was established by ventilation/perfusion scan, pulmonary angiogram, or autopsy. Mortality among patients with PE was 34%. Using a case-control method, preoperative and postoperative risk factors for PE were identified by multivariate and multiple logistic regression analyses. Preoperative risk factors included bed rest ($p < 0.003$), prolonged hospitalization before operation ($p < 0.004$), and cardiac catheterization performed through the groin within 15 days before operation ($p < 0.01$). Postoperative risk factors were congestive heart failure ($p < 0.008$), prolonged bed rest ($p < 0.05$), and deep vein thrombosis ($p < 0.03$). This study demonstrates that PE is an unusual complication after cardiac operations, has a high mortality rate, and is often related to perioperative immobility and recent groin catheterization. These results also suggest that minimizing preoperative hospital stay may be important in PE prophylaxis.

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Pulmonary embolism (PE) is a common disease, affecting approximately 700,000 Americans annually and causing death in 20% to 40% [1, 2]. Fifty percent of recognized PEs occur in hospitalized patients, often as a complication after operation [2]. Among general surgical patients, the incidence of fatal postoperative PE is 0.8% to 1.0% [1, 3–5]. Pulmonary embolism may be less common after cardiac operations [6–9]. This retrospective review was undertaken to determine the incidence of PE after cardiac operations at the Johns Hopkins Hospital and to identify risk factors unique to this patient population.

Material and Methods

Patient Population

Between January 1, 1985, and December 31, 1989, 5,694 adult patients (18 years or older) had open heart surgical procedures at the Johns Hopkins Hospital. To identify those patients with PE, reports from morbidity and mortality conferences, all pulmonary ventilation/perfusion scans, all pulmonary angiograms, and all autopsies were reviewed. Criteria for PE were: ventilation/perfusion scan read as "high probability," positive pulmonary angiogram, or autopsy findings of PE. Thirty-two patients with PE within 60 days of a cardiac opertion were identified. Each patient was then matched with a control adult patient who underwent operation on the same day, in most cases by the same surgeon in the same operating room.

Chart Review

Data collected on each patient included operative procedure, presence of established risk factors for PE (bed rest, history of PE or deep venous thrombosis, diabetes, peripheral vascular disease, obesity, congestive heart failure, malignancy, varicose veins, female sex, black race, recent myocardial infarction, and lower extremity instrumentation), antiplatelet or anticoagulation regimen, and clinical presentation of PE. Complete medical records were reviewed in detail.

Statistical Analysis

Risk factors for PE were analyzed by univariate and multiple logistic regression analyses. For the univariate analysis, cross-tabulations of discrete variables by case-control status were assessed using Fisher's exact test, and mean values for continuous variables were compared using the unpaired t test. All p values are two-tailed; a p value of 0.05 or less was considered statistically significant. Multiple logistic regression was used to evaluate the variables that appeared to be important by univariate analysis; these variables were added singly to a null model that already contained age, sex, obesity, varicose veins, and recent myocardial infarction. Due to small stratum sizes, each emergent risk factor was only considered separately. The maximum likelihood estimates of the odds ratio were assessed by the likelihood ratio test, comparing the extended model with the risk factor of interest added to the null model [10]. For the multiple regression analyses, the median value was used as the cut-off point to dichotomize the continuous variables (age,

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Table 1. Operative Procedures

Patients	PE Patients	Controls
CABG	23	22
CABG/AVR	2	1
CABG/MVR	0	2
CABG/aortic valvulotomy	1	0
CABG/LV aneurysmectomy	0	1
AVR	2	2
MVR	2	3
VSD repair	1	0
AICD/LV aneurysmectomy	1	0
Left atrial myxoma	0	1
Total	32	32

AICD = automatic implantable cardiac defibrillator; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; LV = left ventricular; MVR = mitral valve replacement; PE = pulmonary embolism; VSD = ventricular septal defect.

time between cardiac catheterization and operation, and length of preoperative hospital stay).

Results

Thirty-two patients (20 men and 12 women) satisfied criteria for postoperative PE, an overall PE incidence of 0.56% in our adult cardiac surgical population. Table 1 summarizes the operative procedures performed on PE patients and the controls. Operative procedures in the two groups were similar, with 71.8% of PE patients and 68.8% of controls undergoing isolated coronary artery bypass grafting.

Table 2. Preoperative Risk Factors, Univariate Analysis

Factor	Cases	Controls	p Value[a]
Bed rest	16	4	0.0025
Preoperative hospital days[b]	5.3 ± 4.5	3.1 ± 5.0	0.063[c]
Myocardial infarction	6	1	0.10
Time from catheterization to operation[b] (d)	24.7 ± 39.9	44.9 ± 63.8	0.13[c]
Varicose veins	7	2	0.15
Age (y)[b]	66.0 ± 8.8	68.1 ± 9.1	0.20[c]
IABP	4	1	0.35
Obesity	11	7	0.41
Malignancy	1	3	0.61
Congestive heart failure	8	10	0.78
Female sex	12	10	0.79
Diabetes	6	8	0.73
History of DVT	3	2	1.0
Peripheral vascular disease	2	1	1.0
Black race	3	3	1.0

[a] Fisher's exact test, except where indicated. [b] Values expressed as mean ± standard deviation. [c] t test.

DVT = deep venous thrombosis; IABP = intraaortic balloon pump; myocardial infarction = myocardial infarction in 30 days preceding operation; obesity = weight greater than 120% ideal body weight.

Table 3. Postoperative Risk Factors, Univariate Analysis

Factor	Cases	Controls	p Value[a]
Congestive heart failure	13	3	0.008
DVT	6	0	0.024
Reoperation for hemorrhage	3	0	0.11
IABP	3	0	0.24
Bed rest >3 days	19	10	0.044
Coumadin (warfarin sodium)	3	8	0.18

[a] Fisher's exact test.

DVT = deep venous thrombosis; IABP = intraaortic balloon pump.

Pulmonary emboli were recognized on average on postoperative day 13 (standard deviation, 8.2 days; range, 2 to 32 days). Twenty patients (62%) were still in the hospital at the time of the PE. Sixty-two percent of emboli were documented by ventilation/perfusion scan (20 patients). In 4 patients (11%) the ventilation/perfusion scan was indeterminate, and pulmonary angiography demonstrated PE. The remaining 8 cases (25%) were diagnosed at autopsy. Twelve of 32 patients with PE died; in 11 of these, PE was judged by the clinician or pathologist to contribute substantially to the patient's death. Thus, mortality attributable to PE was 34%. Three patients in the control group died, an operative mortality of 9.4%. The overall mortality on the adult cardiac surgical service at the Johns Hopkins Hospital is 2% [11].

Table 2 contains a univariate analysis of preoperative risk factors for PE. Except for time between cardiac catheterization and operation, these factors have all been shown in other studies to increase the risk of pulmonary embolism [1, 3, 12–17]. In this analysis, only preoperative bed rest was statistically significant. Length of preoperative hospital stay and recent myocardial infarction bordered on significance. Of the 16 patients at preoperative bed rest, 14 were in the coronary care unit. This subgroup of patients may have been at increased risk, with an average duration of preoperative bed rest of 6.9 days. Eleven of these patients received intravenous heparin and 4 had intraaortic balloon pumps placed preoperatively.

By univariate analysis, postoperative risk factors for PE were congestive heart failure, deep venous thrombosis, and extended bed rest (Table 3). Three patients who suffered PE had undergone emergent return to the operating room for postoperative bleeding; as a risk factor for PE, the reoperation for bleeding was of borderline significance. Postoperative warfarin sodium (Coumadin) therapy displayed a modest inverse association with PE. Antiplatelet regimens were similar in the two groups, with most patients receiving aspirin and dipyridamole after coronary artery bypass grafting.

Table 4 contains analysis of selected preoperative and postoperative risk factors after multiple regression analysis adjusted for age, sex, obesity, presence of varicose

Table 4. Preoperative and Postoperative Risk Factors, Multiple Logistic Regression Analysis

Factor	Odds Ratio	*p* Value[a]
Preoperative		
Preoperative bed rest	6.0	0.011
>1 Hospital day	6.0	0.003
<15 Days cath to OR	5.0	0.008
Postoperative		
Postoperative congestive heart failure	7.9	0.007
Bed rest >3 days	4.83	0.015
Coumadin (warfarin sodium)	0.4	0.250

[a] Likelihood ratio test, adjusted for age, sex, obesity, varicose veins, and a history of myocardial infarction in the 30 days preceding operation.

cath = catheterization; OR = operating room.

veins, and history of recent myocardial infarction. This analysis demonstrated that preoperative bed rest, longer preoperative hospitalization, recent cardiac catheterization, postoperative congestive heart failure, and prolonged postoperative bed rest were associated with increased risk of postoperative PE. A second surgical procedure, postoperative deep venous thrombosis, and presence of an intraaortic balloon pump could not be examined in this model because none of these factors were present in control patients.

Comment

From 1985 to 1990, 0.56% of adult patients undergoing open cardiac surgical procedures at the Johns Hopkins Hospital suffered PE. This group constitutes the largest reported series of patients with PE after cardiac operations, and offers a unique opportunity to identify specific risk factors. Other authors have documented an incidence of 0.52% to 3.5% [6–9]. Rao and associates [18] reported an incidence of nearly 10%, but all patients in their series had indwelling lower extremity arterial and venous catheters during the first 3 postoperative days. The relatively low incidence of PE after cardiac operations has been attributed to intraoperative heparinization and postoperative anticoagulation or antiplatelet therapy [6]. In addition, cardiopulmonary bypass causes changes in blood elements that may retard clot formation; these changes include consumption of coagulation factors, activation of the fibrinolytic cascade, thrombocytopenia, platelet dysfunction, and hemodilution [13, 19]. In spite of these phenomena unique to cardiac operations, a small but significant number of patients suffer PE in the postoperative period. Furthermore, mortality attributable to PE is 34% in this series. Others have reported mortality ranging from 0% to 38% [6, 7, 18].

Only two risk factors for PE specific to the cardiac surgical patient have been described previously: hyperlipidemia and repair of atrial septal defect. Hanson and Levine [6] reported that 7% of patients with type II hyperlipidemia suffer PE after cardiac operations. A hypercoagulable state has been postulated in these patients [6, 20]. Preoperative lipid profiles were not available for most of our patients, so the incidence and significance of hyperlipidemia in this population could not be determined.

Howe and associates [7] identified a second group of cardiac surgical patients at risk for PE. They found that PE occurred in 1.5% of patients after repair of atrial septal defect. Patients older than 40 years of age with atrial fibrillation were at even greater risk for PE. Data from Hanson and Levine [6] supported these findings. In contrast, during a 5-year period at the Johns Hopkins Hospital none of the 99 patients undergoing atrial septal defect repair had PE.

Although the population of PE patients was small, certain conclusions can be drawn from the data in this report. As in general surgical patients, PEs in cardiac surgical patients tend to be recognized during the second postoperative week [21]. That most PEs occurred after coronary artery bypass grafting reflects the prevalence of this operation in cardiac surgical practice. Although no particular surgical procedure carried an increased risk of PE in this series, univariate and multiple logistic regression analyses did reveal specific patient-related risk factors for PE. These included preoperative bed rest, longer hospitalization before operation, recent cardiac catheterization, postoperative bed rest, congestive heart failure, and deep venous thrombosis. It is of particular interest that prolonged preoperative bed rest emerged as a risk factor in both analyses. A prospective study of general surgical patients revealed that deep venous thrombosis develops in up to 20% of patients in the hospital awaiting operation [22]. Sigel and associates [23] found that 40% of postoperative deep venous thromboses actually form in the preoperative period and that preoperative inactivity is a significant risk factor for postoperative deep venous thrombosis. Although most patients at preoperative bed rest in our series received intravenous heparin, deep venous thrombosis may form in the heparinized patient [15, 24]. It is possible, therefore, that many patients in this series came to the operating room with preformed deep venous thrombosis. Conditions unique to cardiac operations support this hypothesis. Heparinization, coagulopathy, hemodilution, and thrombocytopenia associated with cardiopulmonary bypass probably decrease the risk of intraoperative deep venous thrombosis. In addition, anticoagulants and antiplatelet agents administered postoperatively may afford further protection from thromboembolic disease [25]. Thus, for those patients already in the hospital awaiting operation, the preoperative period may be a time of particular vulnerability to deep venous thrombosis formation.

Although PE is an unusual complication after cardiac operations, it is associated with high mortality. It follows that all reasonable means of prophylaxis be applied to high-risk patients. These data suggest that reducing preoperative hospitalization in patients awaiting urgent operation should be considered an important component of PE prophylaxis.

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DISCUSSION

DR HARVEY W. BENDER, JR (Nashville, TN): I enjoyed your presentation very much. I have a couple of questions. If I understood you right, you confirmed the diagnosis in 60% of the patients with a ventilation/perfusion scan alone. Is that correct?

DR GILLINOV: That is correct. In 62% of our patients, the ventilation/perfusion scan was read as "high probability," and the diagnosis of pulmonary embolism, which was suggested by the patient's clinical course, was considered confirmed.

DR BENDER: It has been my bias that the ventilation/perfusion scan, particularly in the early postoperative period in cardiac surgical patients, is fairly unreliable. Do you have more data to suggest that that is wrong?

DR GILLINOV: It is true that the ventilation/perfusion scan is more difficult to interpret if there is underlying pulmonary pathology. Certainly all patients in this series had some degree of pulmonary injury as a result of sternotomy and cardiopulmonary bypass. However, by postoperative day 13, the average time of diagnosis of pulmonary embolism, much of this pulmonary injury will have resolved. Ventilation/perfusion scans were considered definitive evidence of pulmonary embolism only if they were read as "high probability" by the radiologist. In 4 cases, the ventilation/perfusion scan was indeterminate and pulmonary embolism was confirmed by pulmonary angiography. In the remaining cases, pulmonary embolism was demonstrated at autopsy.

DR BENDER: How many of these pulmonary emboli were hemodynamically significant? You may have said that and I might have missed it.

DR GILLINOV: Eleven patients died as a result of their pulmonary emboli, usually secondary to dramatic cardiac and respiratory compromise. There was some hemodynamic compromise in approximately 50% of patients.

DR MICHAEL W. GALLAGHER (Houston, TX): I enjoyed your presentation very much. Have you related this to heparin-induced thrombocytopenia? Recently we have had 2 patients who have had serious pulmonary emboli, both of whom had heparin-induced thrombocytopenia. Have you looked at this in any way in this series?

DR GILLINOV: That is an interesting question. We have not examined that; however, in light of the recent data presented concerning thrombocytopenia and heparin-related antibody, we think it would be very interesting to look at that.

Randomized Trial of Neoadjuvant Therapy for Lung Cancer: Interim Analysis

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The role of neoadjuvant chemotherapy in stage IIIa non–small cell lung cancer remains undefined. Since 1987, 27 patients with non–small cell lung cancer, all with histologically confirmed metastases to the ipsilateral mediastinal lymph nodes, have been enrolled in an ongoing prospective, randomized trial at our institution. Thirteen patients have been randomized to preoperative etoposide-platinum (EP) chemotherapy-surgery-postoperative EP, and 14 other patients have been randomized to surgery-postoperative mediastinal irradiation (SRT). Both groups are similar in sex, age, weight loss, tumor location, preoperative pulmonary function, physiologic grade, and tumor histology. Eight of the 13 EP patients have responded as evidenced by a 50% or greater radiographic tumor shrinkage after two cycles. Complete tumor and nodal resection rates were similar: 11/13 EP patients versus 12/14 SRT patients. There was no operative mortality for the 27 patients. Median potential follow-up is 29.9 months for the EP group and 34.9 months for the SRT group. Preliminary results suggest a trend toward increased survival time for the EP group (median, 28.7 months) versus the SRT group (median, 15.6 months) ($p_2 = 0.095$). Eleven of 12 resected SRT patients have had recurrence versus 8 of 11 resected EP patients. Time to recurrence reveals no significant differences between the two groups but a trend toward increased disease-free interval in the EP group (12.7 months versus 5.8 months, EP versus SRT). This interim analysis demonstrates the feasibility of such a trial; however, despite the trends, definitive conclusions await further accrual and study maturation.

(Ann Thorac Surg 1992;53:992–8)

The management of higher stage non–small cell lung cancer (NSCLC) has been the subject of a number of phase II trials since the early 1980s, although the first single-institution trial of preoperative chemotherapy for lung cancer was begun in the late 1950s at the Chiba University Lung Cancer Institute [1]. Numerous regimens have been evaluated including etoposide-cisplatinum [2]; mitomycin-c, vinblastine, and cisplatinum [3]; and 5-fluorouracil and cisplatinum [4]. Moreover, radiation was added in some phase II trials to provide greater control in the mediastinum, as well as to take advantage of the radiation sensitizing properties of certain chemotherapeutic drugs. The inability to compare studies due to heterogeneity of the stage IIIa population (ie, T3 N0, T1–2 N2) has been recently decreased due to the compulsive use of invasive staging to document the status of mediastinal nodal disease. Despite the multitude of phase II trials, a phase III trial that attempts to evaluate the role of neoadjuvant chemotherapy in a relatively uniform population of patients, all of whom receive appropriate resection and concomitant lymph node dissection, has been lacking. This report summarizes an ongoing phase III trial conducted at the National Cancer Institute, National Institutes of Health, since May 1987 comparing preoperative and postoperative chemotherapy to surgery plus mediastinal radiotherapy in stage IIIa patients with histologically confirmed N2 disease.

For editorial comment, see page 955.

Methods and Patient Population

The phase III protocol was approved by the Clinical Research Subpanel of the National Cancer Institute and the Clinical Center of the National Institutes of Health in October of 1986 (Clinical Center #86-C-205). Patients were recruited for the study in the intramural program of the Surgery Branch, Clinical Oncology Program, Division of Cancer Treatment in Bethesda, Maryland. Eligibility requirements included the diagnosis of NSCLC, with histologic documentation of ipsilateral mediastinal nodal involvement. This nodal verification could be obtained by mediastinotomy, mediastinoscopy, or Wang needle biopsy. Patients who had undergone diagnostic thoracotomy without resection but with nodal biopsy within 30 days of referral were eligible. All pathologic specimens from referring institutions were reviewed at the NCI for verification of diagnosis of NSCLC. Patients with metastatic disease beyond the regional lobar and mediastinal nodes (ie, N3, stage IIIb), prior malignancy, superior vena caval syndrome, malignant pleural effusion, performance status greater than ECOG 3, prior radiotherapy or chemo-

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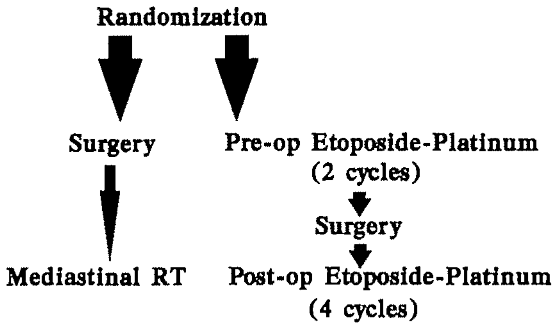

Fig 1. Schema for randomization of patients with stage IIIa non–small cell lung cancer. (RT = *radiation therapy.)*

therapy, or serious medical conditions such as severe pulmonary or renal disease that would render the patients unsuitable for chemotherapy or surgery were excluded.

The preliminary evaluation, in addition to invasive mediastinal staging, included computed tomographic analysis of the chest, abdomen, and brain as well as radionuclide bone scan. Functional criteria measured in all patients included routine pulmonary functions, baseline audiogram, and creatinine clearance. Complete blood count, measurement of serum electrolytes, and hepatic panel were performed at intervals, as dictated by the protocol.

Upon verification of acceptability for protocol entry, patients were randomized to one of two treatment groups, as described below, and were stratified by histologic type, performance status (ECOG), and weight loss (Fig 1).

Neoadjuvant Chemotherapy-Surgery-Chemotherapy (EP group)

Patients randomized to the neoadjuvant arm received two 21-day cycles of etoposide and cisplatinum chemotherapy (Fig 2). Two 21-day cycles were administered in the outpatient clinic, consisting of a bolus of 120 mg/m^2 etoposide on 3 consecutive days and cisplatinum (80 mg/m^2) every 21 days after sufficient hydration and emetic therapy (metaclopromide, benadryl, and dexamethasone). Dose modification for neutropenia and renal or hepatic dysfunction was strictly defined in the protocol. At the completion of the second cycle, just before the operation, a repeat chest computed tomogram was performed to assess response to chemotherapy. Tumor response was defined as follows: complete response = complete disappearance of all tumor-bearing areas; partial response = a 50% or greater reduction in the sum of the products of two perpendicular diameters of all tumor sites; no response = less than a 50% reduction in the sum of the products of the two perpendicular diameters of all tumor sites. Patients were then taken to the operating room for resection of the primary tumor with concomitant lymph node dissection. Postoperatively, patients who responded to chemotherapy received four additional cycles of the same regimen. Patients who did not fulfill criteria for a partial or complete response preoperatively were offered postoperative mediastinal radiation (see below).

Surgery and Postoperative Radiation Therapy (SRT group)

Patients randomized to receive immediate surgery were operated on within 2 weeks of randomization. Briefly, the appropriate resection to establish negative margins was performed in all cases, including, if necessary, sacrifice of contiguous structures (chest wall, pericardium, and vena cava wedge in a solitary case). Both the interlobar nodes as well as the mediastinal nodes were resected as recommended by the North American Lung Cancer Study Group [5]. Postoperatively, 54 to 60 Gy of mediastinal radiation was administered over a 6.5-week period in the outpatient radiation oncology clinic. With extensive treatment planning, spinal cord doses were limited to a total dose of less than 45 Gy using multiple fields of 10 MEv x-rays.

All patients were restaged every 3 months with physical examination, laboratory evaluation, chest roentgenograms, and head, chest, and abdominal computed tomograms. Bone scans were repeated at 6-month intervals.

Statistical Methods

All patients randomized to date have been included in the analysis. Durations of survival or time to recurrence (= disease-free interval) were calculated from date of randomization to date of operation as indicated, until date of death, relapse, or last follow-up. The probability of survival or relapse-free survival was calculated using the Kaplan-Meier method [6]. The significance of the differences between pairs of Kaplan-Meier curves was computed by the Mantel-Haenszel technique [7]. Fisher's exact test was used to evaluate the significance of the difference between two proportions. All p values are two-sided and denoted by p_2.

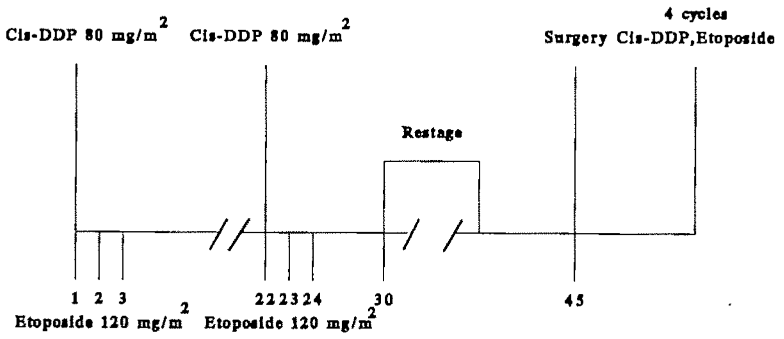

Fig 2. Schema for the etoposide-platinum (Cis-DDP) *treatment arm of the randomized protocol.*

Table 1. Patient Characteristics

Variable	EP	SRT
Male/female	4/9	8/6
Age (y)	51 ± 3	55 ± 2
Weight loss > 5%	1/13	1/14
Location (left/right)	6/7	5/9
PFT		
FEV$_1$ (%)	75 ± 7	76 ± 4
FVC (%)	79 ± 5	81 ± 4
Histology		
Adenocarcinoma	7	8
Epidermoid	3	3
Large cell	3	3

EP = etoposide-platinum/surgery/etoposide-platinum; FEV$_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity; PFT = pulmonary function tests; SRT = surgery/radiation therapy.

Results

From May 1987 to July 1991, 27 patients were randomized on the protocol. The full protocol accrual requirement was for 148 patients to detect a 20% improvement in 5-year survival as a result of chemotherapy. However, due to the selectivity of the patient population and single-institution construction of the trial, accrual was much slower than anticipated. There were 12 men and 15 women, of whom 13 randomized to chemotherapy and 14 randomized to immediate operation. As seen in Table 1, there were no differences with regard to functional status, age, location of the primary tumor, or histologic subtypes in either group. Histologic confirmation of N2 disease was obtained by mediastinoscopy in 13 patients, Wang needle biopsy in 3, mediastinotomy in 9, prior thoracotomy in 1, and percutaneous transthoracic needle biopsy in 1. Sixty-three percent (17) of the patients were symptomatic.

Chemotherapy Group

All 13 chemotherapy patients (100%) received full dose chemotherapy, and all of this treatment was delivered in the outpatient clinic. Alopecia (13/13) was the most common complication.

Eight patients (62%) had a roentgenographic partial response; all other patients had a marginal (2) or no response (3). Patients underwent resection 47 ± 1 days after initiation of chemotherapy, as called for in the protocol. Chemotherapy was reinstituted a mean of 46 ± 11 days after the operation, and 24 of 32 predicted cycles were delivered. Of the 8 preoperative responders, 6 received 100% of the preoperative and postoperative chemotherapy. One patient refused further chemotherapy, whereas chemotherapy was terminated after four cycles in another patient because of deterioration of renal function. In all 50 cycles of chemotherapy, 4 patients required admission: 3 for dehydration due to chemotherapy-related nausea and vomiting, and 1 because of neutropenic fever.

Complications and Mortality of Operation

There were no postoperative deaths in either the EP or SRT groups. Additionally, we found no objective difference in the conduct of the operation whether or not the patients had received preoperative chemotherapy. Two EP patients had unresectable disease. Both were found to have stage IIIb disease at exploration, one with diffuse pleural carcinomatosis and a second with a malignant pericardial effusion. Two patients in the SRT group had unresectable disease because of mediastinal invasion and were reclassified as IIIb. There were no significant differences between the two groups in the magnitude of procedure required to establish negative margins (pneumonectomy: 3 versus 5; lobectomy: 7 versus 6; lobectomy and chest wall resection: 1 versus 1; unresectable: 2 versus 2; EP versus SRT, respectively). Postoperative complications in the chemotherapy group included deep venous thrombosis (1), recurrent nerve transection (1), and arrhythmia (1). One patient each in the SRT group suffered pericarditis, hoarseness, and arrhythmia. Another SRT patient had dehiscence of his sleeve resection 3 months after receiving radiation therapy, which necessitated completion pneumonectomy from which he recovered without incident.

Pathologic Findings

There was only one histologic complete response in a patient with adenocarcinoma who underwent chest wall resection and upper lobectomy. No tumor was found in the surgical specimen, including the lymph nodes. Nevertheless, the patient had recurrence 7 months later in the ipsilateral supraclavicular nodes. All other patients were found to have residual tumor of the same histologic cell type as when they were first entered on protocol. Although a higher proportion of the patients were found to have nodal positivity in the immediate surgery group (N1, 7/11 versus 10/12, EP versus SRT; N2, 6/11 versus 12/12, EP versus SRT), no significant differences were seen at this time.

Table 2 details the preoperative clinical staging of the two groups of patients before resection as well as the final pathologic staging based on complete nodal sampling and examination of margins (all of which including bronchial, vascular, and chest wall were negative for tumor in the 23 resected patients). Because complete nodal sampling was performed after therapy in the EP group, it is difficult to relate levels and location with prognostic significance for these patients.

Survival and Recurrences

The median potential follow-up for the EP group is 29.9 months, compared with 34.9 months for the SRT group. The 18-month survival probability estimate for all patients (n = 27) is 59.7%, with a 95% confidence interval from 40.1% to 76.7%. This did not differ much from the 18-month survival estimate of 63.7% for the 23 resected patients (median survival, 21.3 months) (Fig 3). At this interim analysis, there is no significant difference in survival since randomization of the EP versus the SRT group, with the former having a median survival of 28.7 months versus 15.6 months for the latter ($p_2 = 0.095$) (Fig 4). For this interim analysis, a p value of no more than 0.01 would have been needed to consider declaring a significant result before reaching the planned accrual, and thus

Table 2. Preoperative and Postoperative Pathologic Staging for the 23 Patients With Total Resection

Chemotherapy-Surgery-Chemotherapy			Surgery and Postoperative Radiation Therapy		
Preresection Stage	Postresection Stage	Number of N2 Levels Positive for Tumor	Preresection Stage	Postresection Stage	Number of N2 Levels Positive for Tumor
T2 N2	T2 N2	2	T2 N2	T2 N2	1
T2 N2	T2 N0	0	T2 N2	T2 N2	1
T3 N2	T0 N0	0	T2 N2	T2 N2	2
T2 N2	T1 N2	2	T2 N2	T2 N2	3
T2 N2	T2 N2	2	T3 N2	T3 N2	2
T2 N2	T4 N0[a]	0	T2 N2	T2 N2	1
T2 N2	T2 N0	0	T2 N2	T2 N2	1
T2 N2	T2 N2	2	T2 N2	T2 N2	2
T2 N2	T1 N0	0	T2 N2	T2 N2	2
T2 N2	T2 N2	3	T2 N2	T2 N2	1
T2 N2	T2 N2	2	T2 N2	T2 N2	1
			T2 N2	T2 N2	2

[a] Partial resection of superior vena cava.

this merely indicates a trend. A selected analysis of the survival since randomization for the 8 responders versus the 14 SRT patients reveals a median survival of 28.7 months and 15.6 months, respectively ($p_2 = 0.073$) (Fig 5). However, this analysis is best viewed descriptively because this is a selected comparison and responders needed to survive long enough to be classified as responders. Possibly, a more legitimate method would be to compare EP responders with SRT patients from the date of operation as all patients are known to be either chemotherapy responders or treated with surgery plus radiation therapy at the operation date. Nevertheless, the difference in survival from the date of operation was also not yet statistically significant despite a trend toward increased survival in the chemotherapy responders ($p_2 = 0.076$). Of course, this is also a selected comparison which needs to be interpreted with caution.

Of the 23 resected patients, 19 have had recurrence (83%). Eleven of 12 resected SRT patients (92%) and 8 of 11 resected EP patients (73%) have had recurrence ($p_2 = 0.52$). The initial site of treatment failure in the SRT group was systemic in 10 (91%); 1 additional patient had locoregional recurrence (9%). In contrast, 63% (5/8) of the EP patients had locoregional recurrence, and 37% (3/8) failed initially systemically ($p_2 = 0.048$). Overall, the brain was the most frequent site of recurrence (7/19; 37%), followed by the locoregional nodes (6/19; 31%) and bone (5/19; 26%).

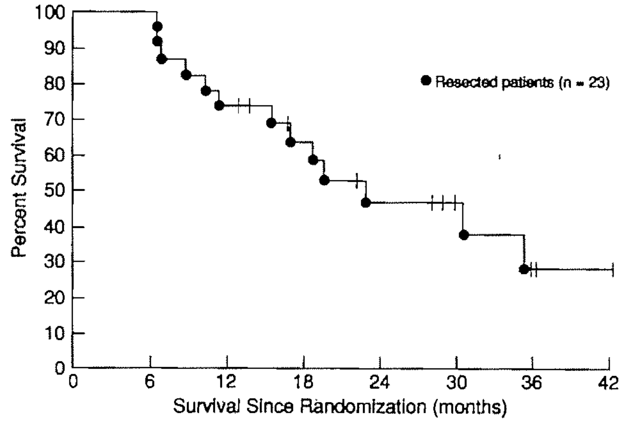

Fig 3. Survival of the 23 patients in the protocol who had complete resection of disease: median survival was 21.3 months from the time of randomization.

Time to recurrence (or disease-free interval) since randomization revealed no significant differences between the two groups ($p_2 = 0.083$) despite a trend toward longer disease-free intervals in the EP group. The 4 patients with unresectable disease were considered to have failed at their date of operation. Analysis of the responders to EP revealed an even greater trend toward increased disease-free interval compared with the SRT group from the time of randomization ($p_2 = 0.047$) or from the time of operation ($p_2 = 0.065$). These comparisons were both selected ones, and have potential bias because of the lead time for response as well as the several week difference in time of operation after randomization between the two groups.

No differences in survival or relapse were found be-

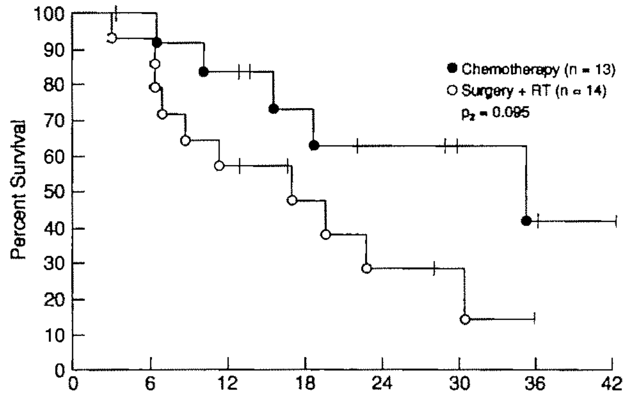

Fig 4. Survival of the EP group compared with the SRT group.

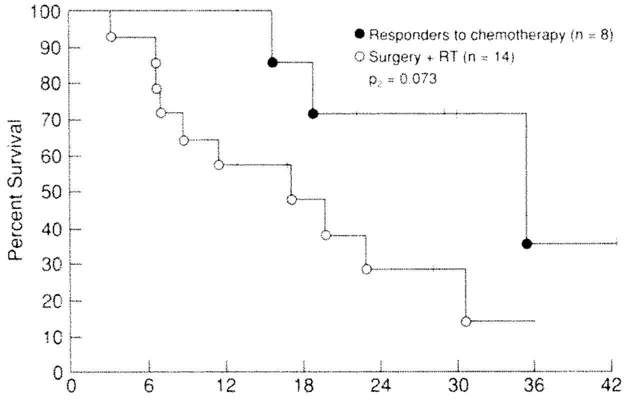

Fig 5. Survival of the 8 EP patients who had a major roentgenographic response compared with the SRT group.

tween the major histologic groups. Patients with large cell lung cancer or epidermoid histology who were randomized to EP (n = 7) had a trend toward increased survival since randomization over the same histologies randomized to immediate operation (n = 6; p_2 = 0.09) (Fig 6). A similar trend was not seen comparing the 6 adenocarcinoma patients randomized to EP with the 8 SRT adenocarcinoma patients (p_2 = 0.57).

Comment

The concept of neoadjuvant therapy for higher stage NSCLC has become almost an obsession with thoracic and medical oncologists. The recognition of agents effective in NSCLC, especially in disease limited to the hemithorax, has resulted in a plethora of phase II trials trying to identify the population of these patients who would exhibit prolonged survival and freedom from recurrence [8]. Multiple regimens, with and without mediastinal radiation, have been investigated. As stated previously, the heterogeneity of populations studied, entrance criteria with regard to invasive mediastinal staging, and intraoperative conduct of lymphadenectomy have made these studies difficult to interpret. Moreover, the absence of a nonhistorical control group with which to compare the possible effect of the adjuvant therapy only prolongs the agony of trying to definitively answer the question of neoadjuvant utility.

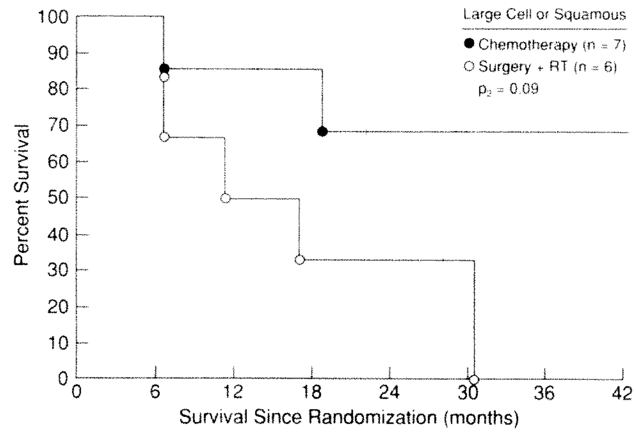

Fig 6. Survival of patients with large cell or epidermoid cancer who received or did not receive etoposide-cisplatinum neoadjuvant therapy.

These difficulties not only persist, but also were present in 1987 when this study was initiated. Therefore, despite the possibility of poor accrual we attempted to design a single-institution study that could possibly elucidate the role of "upfront" therapy in NSCLC. There were certain criteria, however, that made the study unique at the time of inception including the insistence of a positive mediastinal nodal biopsy for entrance. From the International Staging System Survival curves, and as corroborated by the Japanese [9], we realized that T3 N0 disease was distinctly different in survival from T1–3 N2 disease; hence, entrance into the program was restricted to patients with N2 node involvement.

We chose EP as the neoadjuvant routine because it is better tolerated and can be administered in an outpatient setting [10]. A truly effective neoadjuvant program, in our opinion, is one that not only gives consistent response rates but also is well tolerated by the patients. Etoposide-cisplatinum, compared with vinblastine and 5-fluorouracil-cisplatinum, had comparable response rates for limited disease. Furthermore, EP did not require extremely high doses of drugs and could be delivered on an outpatient basis (important issues in preserving quality of life and minimizing hospital costs). Moreover, the design of the study was "time-limited" in that only two cycles would be delivered preoperatively. It was important to deliver these cycles efficaciously to allow timely graduation to the operating room so that the patients' disease would not become unresectable if it progressed.

Probably the most ambitious portion of the trial design was the insistence of a surgery control arm. Thus, all patients had to have a resection option, albeit aggressive, at study entry. This mandated careful study of the computed tomograms of the chest, and correlation with referral notes when the invasive staging was not performed at the NCI. By definition only a select group of patients were eligible as all patients with presumed IIIb disease were excluded. One patient in the chemotherapy arm who had had a response to chemotherapy was found to have disease requiring segmental resection of the vena cava (T4) after a true partial response. He completed the protocol and was therefore included in the analysis.

One could argue that the addition of radiation to the "standard treatment group" was not in the best interests of the study. In light of the studies by the Lung Cancer Study Group [11], however, which document decrease in the local recurrence rates by postoperative radiation therapy after resection of higher stage NSCLC without influencing long-term survival, we felt justified in the addition of the mediastinal radiation. One could argue that this arm could have been just as easily treated without radiation; however, as described in the results, the disparity of local versus systemic recurrences seen between the two groups (EP versus SRT) may not have been appreciated.

The chemotherapy regimen was well tolerated. Few patients had complications and these were reversible. The necessity for in-hospital resources was minimal. Moreover, all of the chemotherapy was delivered under the auspices of the surgery branch of the NCI, in the Surgery Branch Outpatient Clinic. There was no involvement of other disciplines in the delivery of treatment, ie, medical oncology, and therefore routine follow-up and management of these patients was consistent and easy to perform. This emphasizes the ability of thoracic oncologic surgeons to play more of a role than just technicians in the management of these patients.

The response rate of 62% is comparable with that of other regimens used (vinblastine, 5-fluorouracil-cisplatinum). The other regimens, however, seem to be associated with greater toxicity, specifically myocardial and pulmonary [12], and required greater inpatient involvement. The solitary histologic complete response was less than that seen with other regimens; however, the size of this study must be taken into account when defining this parameter. Moreover, the value of the histologic complete response in affording a survival advantage is not fully established in the literature for this population of patients. In our 1 case, the patient had local recurrence in the mediastinum despite the histologically negative tumor bed and nodal basin.

The only thoracic surgeon involved in this study was the principal investigator (H.P.). The ability to perform complete resection in these patients probably reflects the homogeneity in the selection of the IIIa group. Only 15% of the patients explored (2 from each group) were found to have "unresectable" IIIb disease. The disease therefore could be completely resected to the surgeon's satisfaction after pulmonary resection and lymphadenectomy. Any opinions regarding the degree of difficulty of these operations, operative results, or patient management decisions remain uncontrolled by other observers. Nevertheless, in our series, there was no difference in the difficulty or magnitude of resection, conduct of operation, or estimated blood loss. Both the CT and the SRT groups had comparable lengths of operation and duration of hospital stay, and neither group suffered operative mortality. Moreover, in neither group was any patient left with a positive margin at the completion of the resection, and the extent of resection was comparable. Therefore, at least with EP, one cannot conclude that preoperative chemotherapy affects the ability to conserve pulmonary parenchyma.

Despite the trend toward a decreased number of patients in the chemotherapy group with N2 or N1 involvement at resection, and the uniformity of lymph node dissection in these patients (one surgeon, one technique), one cannot say that this truly represents "downstaging" of disease due to the small number of patients in the series. It is interesting, however, that the majority of the recurrences in the chemotherapy group were locoregional (but extrathoracic), and the majority of the recurrences in the SRT group were systemic. This finding titillates the imagination in that perhaps the addition of preoperative or postoperative radiation therapy might have an impact on these local recurrences in future studies.

This study is only at interim analysis with regard to survival. Nevertheless, the median survival of all resected patients (21.3 months) is significantly better than that in other studies of IIIa NSCLC patients with clinical N2 M0 disease. We found no difference at this time in survival from time of randomization, yet the disease-free interval has a trend toward increased time to recurrence in the EP group. This is vaguely reminiscent of the findings of the LCSG in a number of studies that investigated postoperative adjuvants after NSCLC resection.

What, then, is the "take-home" message from this study at interim analysis? Certainly, at this time this study does not justify the routine use of neoadjuvant chemotherapy in the management of N2 positive NSCLC patients. Moreover, it is foolhardy to say that the EP regimen is the only or best regimen for these patients, and without doubt, other regimens will give similar response rates [3–5, 12]. It is even possible that more platinum should be delivered for even greater response rates; however, a close scrutiny of Klastersky's work regarding EP would not support this claim, at least in higher stage patients [10]. Nevertheless, there are no phase III trials that compare different regimens for neoadjuvant therapy to each other in a homogeneous group of patients with stage IIIa disease. Furthermore, this study does not imply that preoperative chemotherapy will significantly improve long-term survival in these patients. Despite high response rates, it is too early to define favorable populations that will enjoy the benefits of these responses. The study does reinforce the safety of operating on patients with higher stage lung cancer, and implies that a fixed, but small percentage of patients will be salvaged by operation alone. Although this study continues to accrue patients, it will be the responsibility of the cooperative groups to continue ongoing phase III trials such as this to definitively define the role of neoadjuvant chemotherapy.

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DISCUSSION

DR CAROLYN E. REED (Charleston, SC): I applaud your efforts and I think we all desperately need to join in a multiinstitutional trial. I have several questions for you. One concerns the selection process of your N2 patients. I know a number of the patients are referred to you. Are all these patients sent to you by surgeons who just routinely do mediastinoscopy? The reason I ask this is that one of your arms is surgery alone, and in many of the studies that are reported we are talking about clinical N2 disease, disease that we would not expect to be able to take to surgery and perform a complete resection. In other words, we are using the chemotherapy to make them resectable and you are using surgery alone on this. That is one question. The second question is, as you had an increased local failure rate in an arm that showed decreased systemic recurrence, what do you think the role of radiation therapy should be in that arm? Finally, would you give us some words of wisdom as to what you think would be the ideal multiinstitutional study that we should mount?

DR PASS: Regarding your mediastinoscopy question, approximately 50% of these patients had their nodal disease diagnosed invasively by me. I think the most important thing is the screening of the computed tomographic scan. When you look at enough computed tomographic scans, you can say whether there is going to be gray area, IIIb-IIIa, or whether this is going to be a patient in whom you can perform resection. Personally I think there is not enough emphasis in the literature on that. I think that essentially you ought to be able to define "bulky" versus "nonbulky disease"; also, by doing the mediastinoscopy *yourself* you get the idea whether you are going to be able to resect those nodes.

DR REED: What is going to be the role of radiation therapy?

DR PASS: I have no idea what the role of radiation therapy is going to be. That is why I wrote the program originally to not even involve that in the up-front treatment. The purpose of this trial was not to look at what radiation therapy does in non–small cell lung cancer up front. I wanted to see how good the chemotherapy was. Now, what the study is showing is that you may have to add something to the chemotherapy for local control.

With regard to the ideal study, I am not so sure that the ideal control is a nonsurgical group. My own feeling is that if you have enough surgeons who operate on these higher stage lung cancer patients, they can sift out which are the real IIIa's with N2 disease and resect them and see if you salvage a fixed number, as opposed to just giving up on them.

DR EDWARD F. PARKER (Charleston, SC): I enjoyed very much this report and your diligence in pursuing this study. I was impressed with the fact that among the survivors with recurrence, apparently the first recurrence was in the cervical lymph nodes. One would wonder if they could have been positive at the start.

Brantigan in Baltimore some years ago showed that in patients with carcinoma of the lung, the ipsilateral nodes on routine biopsy were positive in about 20%, even though they were nonpalpable.

We found some years ago the same thing; we also found that the contralateral nodes were positive for carcinoma in about 20% of the patients even though there was no abnormality on palpation of the neck. What is your opinion of the value of preoperative cervical lymph node biopsy, unilateral or bilateral, in the study of these patients to ascertain, more accurately than we do now, the preoperative staging and the prognosis after excision of the primary lesion?

DR PASS: Dr Parker, I think that is a good question. If you look at the locoregional recurrences, what you see is that many patients fail in supraclavicular nodes. We also have had patients with recurrence in paratracheal and azygos nodes. I am not so sure that routine scalenus or supraclavicular nodal biopsy is going to salvage many more of these patients.

The bigger question, though, is, does this recurrence affect long-term survival, and I do not really have an answer to that question. So if it does not affect long-term survival, I am not so sure whether it is necessary to have the patient submit to concomitant preoperative radiation therapy, which in itself could be toxic.

DR JOE B. PUTNAM, JR (Houston, TX): Dr Pass, I enjoyed your presentation and certainly share your concern for better treatment for lung cancer. Specifically I was interested in your standard criteria for inclusion, how these patients were staged, and your comments on the value of routine brain computed tomograms before operation and also in following up these patients long-term.

DR PASS: I do everything to make sure that these patients are selected as a right homogeneous group. All patients have preoperative computed tomograms of the head, chest, and abdomen, and bone scans in the staging evaluation. You could argue that you are not going to pick up that many patients with silent brain metastases in this group. I personally feel, though, that for study purposes, to answer the question, you must do the preoperative computed tomography.

These patients have follow-up computed tomograms every 3 months to attempt to pick up a recurrence as early as possible. I do not think the studies need to be performed any more often than that.

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Analysis of Determinants of Ventricular Fibrillation Induced by Reperfusion: Dissociation Between Electrical Instability and Myocardial Damage

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To assess the underlying mechanisms of ventricular fibrillation induced by myocardial reperfusion after cardioplegic arrest, 62 patients undergoing an open heart operation were divided into two groups based on the absence (group 1, n = 37) or the development (group 2, n = 25) of reperfusion-induced ventricular fibrillation. There was no close relationship between the incidence of reperfusion-induced ventricular fibrillation and aortic clamp time. On reperfusion, the time to onset of cardiac activity was similar in groups 1 (2.4 ± 1.8 minutes) and 2 (1.9 ± 1.1 minutes). At that time, there was no significant difference in values of arterial oxygen and bicarbonate contents, pH, or base excess between the two groups, but myocardial temperature was significantly higher in group 2 (25.6° ± 3.4° versus 27.6° ± 2.4°C; $p < 0.05$). In addition, serum levels of sodium (123.9 ± 4.2 versus 126.1 ± 3.7 mmol/L; $p < 0.05$) and calcium (0.80 ± 0.07 versus 0.84 ± 0.05 mmol/L; $p < 0.05$) were significantly higher and serum potassium levels (3.98 ± 0.58 versus 3.55 ± 0.61 mmol/L; $p < 0.02$) and the serum potassium to calcium ratio (4.94 ± 0.90 versus 4.29 ± 0.72; $p < 0.01$) significantly lower in group 2. Postoperative serum levels of the myocardial-specific isoenzyme of creatine kinase and myoglobin were similar in both groups. By multivariate analysis, shorter ischemic time, higher myocardial temperature, higher serum sodium concentration, and lower serum potassium to calcium ratio were found to influence induction of reperfusion-induced ventricular fibrillation. We conclude that ion imbalance and myocardial temperature, rather than severity of ischemia-related and reperfusion-related myocardial damage, may be important for the genesis of reperfusion-induced ventricular fibrillation and that reperfusion injury, if reperfusion-induced ventricular fibrillation is a representative phenomenon of reperfusion injury, may not be a major cause of postoperative cardiac dysfunction.

(Ann Thorac Surg 1992;53:999–1005)

Reperfusion-induced arrhythmias have been defined as rhythm disturbances developing as a consequence of abrupt reflow to the myocardium after a period of ischemia [1–3]. Interest in this type of arrhythmia has grown because of its possible relationship to sudden cardiac death in humans [2]. Clinical relevance is suggested to be related to relief of coronary artery spasm [4] and thrombolytic therapy [5]. In addition, reperfusion of the heart after cardioplegic arrest under the condition of cardiopulmonary bypass can cause a rapid onset of ventricular tachycardia or fibrillation requiring electrical defibrillation. In contrast to other experimental and clinical situations, reperfusion in the operative setting is introduced after global ischemia combined with myocardial protection with high-potassium cardioplegia and hypothermia. Therefore, the genesis of arrhythmias it induces may be somewhat different.

Several experimental studies have demonstrated important factors for the occurrence of reperfusion arrhythmias: α-adrenergic receptor [6, 7], ion imbalance [8], heart rate [9], oxygen radical [10, 11], and severity of ischemia [12]. Nevertheless, the underlying mechanism is still controversial.

One study [13] showed that higher plasma potassium and magnesium levels, a shorter reperfusion time, and a lower myocardial temperature were significantly associated with spontaneous resumption of normal cardiac electrical activity after cardioplegic arrest during coronary bypass procedures. However, in that study, patients in whom cardiac electrical activity resumed spontaneously after aortic unclamping included those requiring electrical defibrillation because of a later onset of ventricular fibrillation during reperfusion. This classification of patients without ventricular fibrillation may be inadequate, as the electrophysiological basis of this type of rhythm disturbance is thought to be dependent on the heterogeneity of electrical recovery in the previously ischemic myocardium. Therefore, any electrical instability occurring during the early phase of reperfusion should be treated as reperfusion-induced arrhythmias. We therefore divided patients into two groups based on the absence or presence of ventricular fibrillation requiring electrical defibrillation during early reperfusion. We also studied several variables (serum ion concentrations, myocardial temperature,

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ischemic time, arterial blood gas, and postischemic changes in the serum level of the myocardial-specific isoenzyme of creatine kinase (CK-MB) and myoglobin) to determine the most important factors influencing vulnerability to reperfusion-induced ventricular fibrillation (RVF) during a cardiac operation.

Material and Methods

Sixty-two patients who weighed more than 30 kg and who underwent an open heart operation in Kyushu University Hospital were divided into two groups depending on the absence or presence of intractable ventricular fibrillation early during reperfusion. Thirty-eight of the 62 patients showed spontaneous restoration of cardiac electrical activity immediately on reperfusion after cardioplegic/ischemic arrest and did not require electrical defibrillation (group 1). In 24 patients, ventricular fibrillation developed early during reperfusion and required electrical defibrillation (group 2). No patient in this study spontaneously resumed normal cardiac rhythm after the onset of preceding ventricular fibrillation. However, 2 patients showed ventricular fibrillation requiring electrical defibrillation after spontaneous restoration of cardiac electrical activity during reperfusion, and they were included in group 2. There were no hospital deaths in either group.

Operative Technique

All operations were performed with standard cardiopulmonary bypass techniques and moderate hypothermia (25° to 28°C). After the ascending aorta was clamped, cold cardioplegic solution (10 mL/kg of body weight) was delivered into the aortic root. When aortic regurgitation was present, the coronary orifices were perfused directly. Additional cardioplegic solution (5 mL/kg) was administered every 20 minutes during aortic clamping. The cardioplegic solution was composed of the following: sodium, 87 mmol/L; potassium, 20 mmol/L; calcium, 0.1 mmol/L; chloride, 97 mmol/L; bicarbonate, 10 mmol/L; and glucose, 25 g/L. It was oxygenated and cooled to 4°C before delivery. Myocardial protection was also provided by topical cooling with ice slush. The temperature of the right ventricular free wall was monitored with a thermistor-tipped probe throughout the operation.

After the aorta was unclamped, systemic rewarming was initiated gradually. Any reduced level of serum calcium ion was not corrected for 30 minutes of reperfusion. Calcium was then given just before discontinuation of cardiopulmonary bypass. As already mentioned, when postreperfusion ventricular fibrillation occurred and did not revert, electrical defibrillation was used to regain normal cardiac electrical activity.

Assessment of Results

At the time of onset of spontaneous cardiac electrical activity or ventricular tachyarrhythmia after aortic unclamping, arterial blood was obtained to measure blood gases (arterial oxygen tension, arterial carbon dioxide tension, pH, and base excess) and serum ion concentrations (potassium, sodium, and calcium). Myocardial temperature was also measured. To evaluate the severity and extent of ischemia-related myocardial injury, serum CK-MB activity and myoglobin concentration were measured preoperatively and at 0.5, 1, 3, 6, 12, and 36 hours after reperfusion.

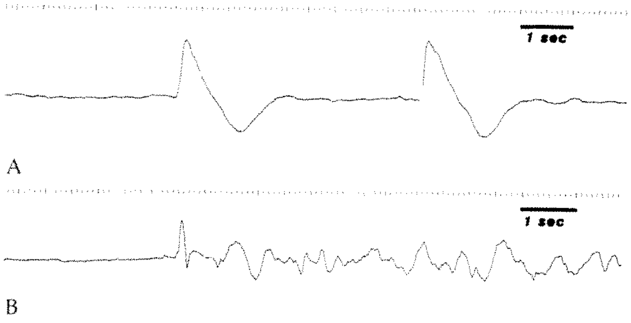

Fig 1. Electrocardiograms from patients with (A) spontaneous resumption of cardiac electrical activity and (B) ventricular fibrillation.

Statistical Analysis

All values were expressed as the mean ± the standard deviation. The significance of difference for the results in the two groups was analyzed using the unpaired Student *t* test. When the *p* value was less than 0.05, the difference was considered significant. In addition, a multivariate regression analysis was used to determine the most important variables causing RVF.

Results

Incidence of Reperfusion Ventricular Fibrillation

Figure 1 shows representative electrocardiograms from patients with spontaneous resumption of cardiac electrical activity (Fig 1A) and development of ventricular fibrillation (Fig 1B). The overall incidence of RVF was 38.7% in this study. The incidence of RVF for each type of operation is shown in Table 1. Seven (29.2%) of the 24 patients who underwent coronary artery bypass grafting had RVF.

Table 1. Incidence of Reperfusion-Induced Ventricular Fibrillation by Type of Operation

Operation	No. of Patients	RVF	Incidence (%)
CABG	24	7	29.2
Valve operation	30	14	46.7
AVR	11	7	63.6
MVR	15	7	46.7
DVR	4	0	0
Operation for CHD	8	3	37.5

AVR = aortic valve, replacement including repeat AVR and Bentall operation; CABG = coronary artery bypass grafting; CHD = congenital heart disease (atrial septal defect and ventricular septal defect); DVR = double-valve replacement; MVR = mitral valve replacement including repeat MVR; RVF = reperfusion-induced ventricular fibrillation.

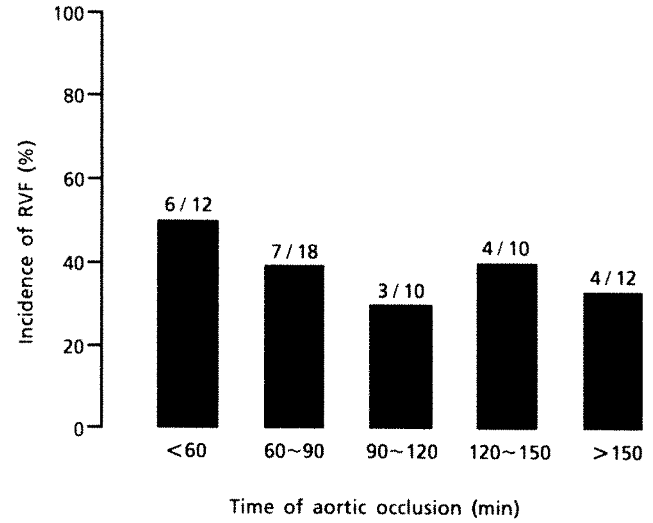

*Fig 2. Relationship between duration of ischemia and incidence of reperfusion-induced ventricular fibrillation (*RVF*) in 62 patients. Numbers above each column represent patients with RVF and total patients in each group.*

The incidence of RVF in patients undergoing a valve operation and in patients having operation for congenital heart disease was 46.7% and 37.5%, respectively. There was no significant difference in the incidence of RVF among patients having any type of cardiac operation. For example, the comparison between the incidence of RVF in patients having bypass grafting and that in patients having aortic valve replacement (29.2% versus 63.6%, respectively; $p = 0.069$) did not reach significance.

Several previous studies [3, 14] as well as two by us [15, 16] reported that the duration of the preceding period of ischemia influenced the vulnerability of the heart to reperfusion-induced arrhythmias. They also demonstrated a bell-shaped relationship between the incidence of RVF and the period of ischemia. However, as shown in Figure 2, there was no clear relationship between duration of ischemia and RVF in the present study.

Age (50.5 ± 15.4 years in group 1 and 50.4 ± 14.2 years in group 2) and body weight (55.3 ± 11.6 kg in group 1 and 53.5 ± 12.6 kg in group 2) were very similar in the two groups. Aortic occlusion time was 110.9 ± 47.8 minutes in group 1 and 91.3 ± 45.0 minutes in group 2 (p = not significant).

Arterial Blood Gases and Serum Ion Concentrations

Figure 3 summarizes the arterial blood gas levels and serum electrolyte concentrations at the time of onset of normal electrical activity or ventricular fibrillation in the two groups. The values for arterial blood gases were almost the same in groups 1 and 2: pH, 7.41 ± 0.06 versus 7.40 ± 0.07; arterial carbon dioxide tension, 28.9 ± 4.8 versus 29.4 ± 4.1 mm Hg; arterial oxygen tension, 335 ± 120 versus 343 ± 149 mm Hg; and base excess, −5.5 ± 2.4 versus −5.5 ± 2.6, respectively. In contrast, there were significant differences in serum concentrations of some cations. Serum sodium and calcium concentrations were significantly higher in group 2 (sodium, 123.9 ± 4.2 versus 126.1 ± 3.7 mmol/L [$p < 0.05$], and calcium, 0.80 ± 0.07 mmol/L versus 0.84 ± 0.05 mmol/L [$p < 0.05$]). The serum potassium level and the serum potassium to calcium ratio were significantly lower in group 2 (potassium, 3.98 ± 0.58 versus 3.55 ± 0.61 mmol/L [$p < 0.02$], and potassium to calcium ratio, 4.94 ± 0.90 versus 4.29 ± 0.72 [$p < 0.05$]). Thus, electrolyte balance in reperfusate is an important factor inducing rhythm disturbance during the early period of reperfusion.

Myocardial Temperature and Time to Onset of Cardiac Rhythm

Figure 4 shows the relationship between time to onset of cardiac electrical activity and myocardial temperature dur-

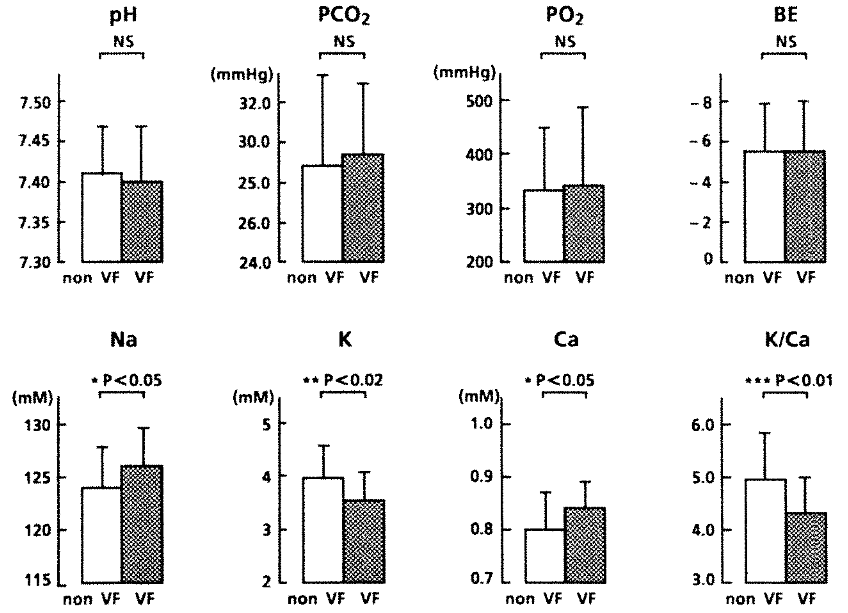

Fig 3. Comparison of arterial blood gas values and serum electrolyte concentrations at the onset of cardiac activity with reperfusion in groups 1 (without ventricular fibrillation; non VF*) and 2 (*VF*). Values are shown as the mean + the standard deviation. (*Ca *= calcium;* BE *= base excess;* K *= potassium;* Na *= sodium;* NS *= not significant;* PCO_2 *= carbon dioxide tension;* PO_2 *= oxygen tension.)*

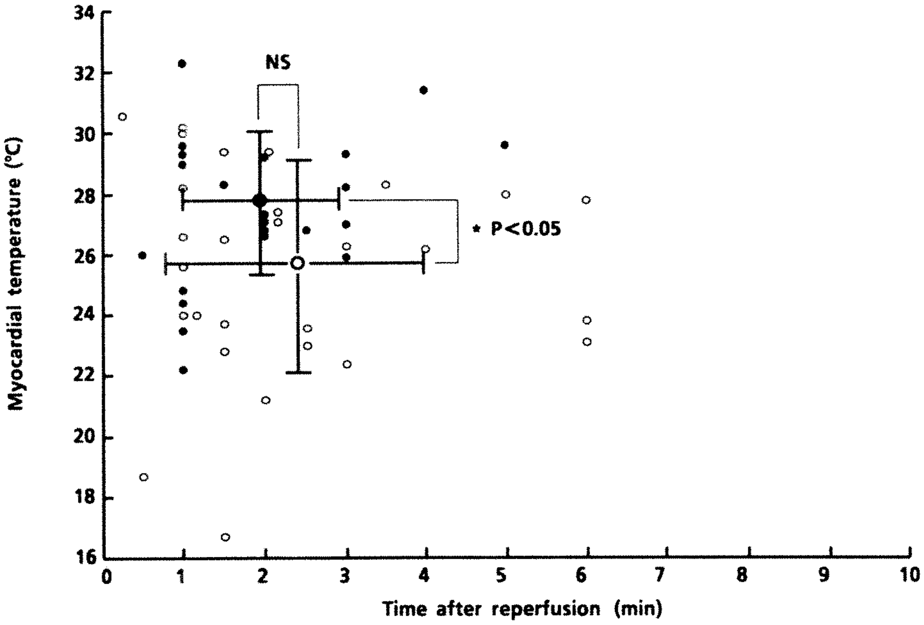

*Fig 4. Comparison of myocardial temperature and time to onset of cardiac activity with reperfusion between groups 1 (○) and 2 (●). Myocardial temperature was measured just when cardiac electrical activity or fibrillation was initiated after aortic unclamping. Values are shown as the mean ± the standard deviation. (NS = not significant; *p < 0.05 between groups I and II.)*

ing reperfusion. The time to onset of electrical excitability (normal beating or fibrillation) was 2.4 ± 1.8 minutes in group 1 and 1.9 ± 1.1 minutes in group 2 (p = not significant). On the other hand, myocardial temperature at that time was significantly higher in group 2 (25.6° ± 3.4°C versus 27.6° ± 2.4°C; $p < 0.05$). The rate of change in myocardial temperature after aortic unclamping was greater in group 2 (4.1° ± 2.7°C/min versus 4.6° ± 4.6°C/min), but the difference was not significant.

Postischemic Myocardial Damage

To evaluate the extent of myocardial damage associated with ischemia and reperfusion, serum CK-MB and myoglobin levels were measured at 0.5, 1, 3, 6, 12, and 36 hours after reperfusion. Serial changes in these concentrations in the two groups are shown in Figure 5. There were no significant differences in either index at any time after reperfusion. The maximum values of serum CK-MB and myoglobin were 112.7 ± 67.8 IU/L and 1,055 ± 750 ng/mL in group 1 and 160.0 ± 165.8 IU/L and 1,388 ± 2,182 ng/mL in group 2, respectively (p = not significant for both). In addition, we [17] recently demonstrated that a prolonged elevation of serum myoglobin levels after reperfusion is highly related to postoperative cardiac dysfunction. However, the changes in the postreperfusion myoglobin level over time were similar in both groups in the present study, and no progressive, persistent increase was seen. These results suggest that the severity of perioperative myocardial damage did not correlate with the vulnerability of the myocardium to reperfusion-induced electrical instability.

Multivariate Analysis of Variables

The variables in the multivariate analysis are given in Table 2. The calculated F value for each factor is also shown. In addition, the most important variables influencing the risk of RVF were analyzed by the forward selection method. A shorter ischemic time, a higher myocardial temperature, a higher serum sodium concentration, and a lower serum potassium to calcium ratio were selected ($Y = -0.0037X_1 + 0.0114X_2 + 0.0446X_3 -$

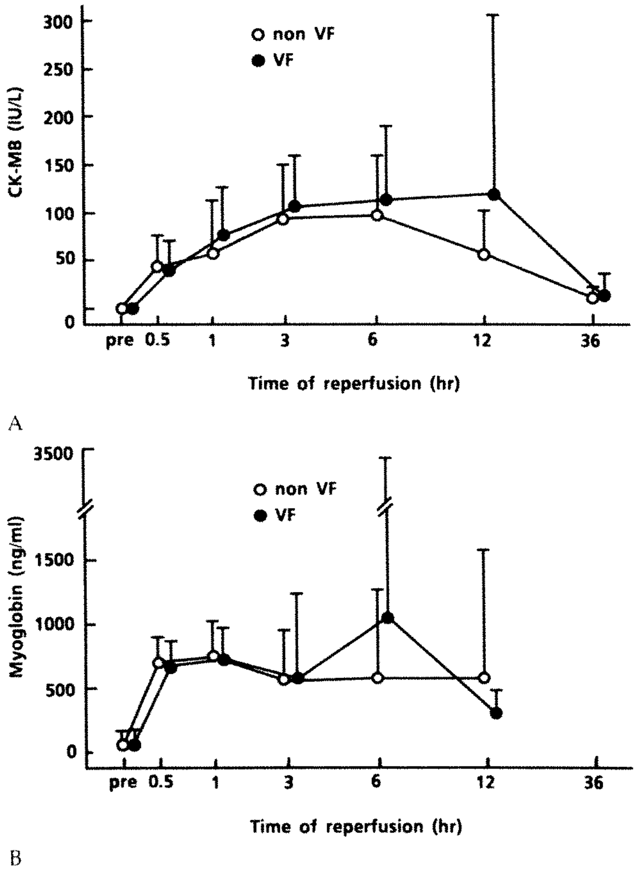

Fig 5. Comparison of postoperative changes in (A) serum levels of the myocardial-specific isoenzyme of creatine kinase (CK-MB) and (B) myoglobin for groups 1 (non VF) and 2 (VF). Data were obtained before operation and at 0.5, 1, 3, 6, 12, and 36 hours after reperfusion. Values are shown as the mean ± the standard deviation.

Table 2. Results of Multivariate Regression Analysis

Factor	*F*-Value	*p* Value
Age	0.078	NS
Body weight	0.438	NS
Aortic cross-clamp time	3.400	NS
Maximum CK-MB	0.764	NS
Maximum myoglobin	1.531	NS
Onset of reexcitation	2.371	NS
Myocardial temperature	3.399	<0.05
Temperature change	1.246	NS
pH	0.207	NS
Pco_2	0.092	NS
Po_2	0.252	NS
Base excess	1.700	NS
Na	3.715	<0.05
K	5.878	<0.05
Ca	2.422	NS
K/Ca	7.661	<0.01

Ca = calcium; CK-MB = myocardial-specific isoenzyme of creatine kinase; K = potassium; Na = sodium; NS = not significant; Onset of reexcitation = time to onset of electrical activity or ventricular fibrillation after reperfusion; Pco_2 = carbon dioxide tension; Po_2 = oxygen tension; temperature change = rate of change in myocardial temperature after reperfusion.

$0.1303X_4 - 4.4616$; $p < 0.05$). These results suggest that perioperative myocardial injury is not a major factor for the development of RVF because a *shorter* period of ischemia was a risk factor, and the postoperative values of plasma CK-MB and myoglobin did not relate to reperfusion-induced dysrhythmias. Alternatively, the presence of RVF was not associated with myocardial damage during the reperfusion period.

Comment

The present study demonstrates that the major correlates of ventricular fibrillation induced by reperfusion are a shorter period of ischemia, a higher myocardial temperature, a higher serum sodium concentration, and a lower serum potassium to calcium ratio. The extent of perioperative myocardial injury, assessed by postoperative levels of serum CK-MB and myoglobin, was the same in patients with or without RVF. In contrast, Bolli and Patel [12] reported three major determinants of reperfusion arrhythmias in dogs with occlusion of the left anterior descending coronary artery: severity of the preceding period of ischemia, amount of ischemic and reperfused myocardium, and heart rate. Their results do not concur with the findings of the present study. Postischemic values of serum CK-MB and myoglobin were not significantly associated with vulnerability of the heart to RVF. Therefore, the severity of ischemia was not an important risk factor for RVF in our series. Elevation of the level of certain enzymes or proteins in the serum has been widely used in the diagnosis of a variety of pathological conditions in the ischemic or infarcted myocardium [18]. We [17] recently demonstrated that the postischemic pattern of myoglobin appearance in the circulating blood is a useful marker to assess postoperative cardiac dysfunction. In patients with a progressive increase in the serum myoglobin level, myocardial injury can be accelerated during the reperfusion period. However, in the present study, the postoperative myoglobin changes in patients with RVF did not exhibit a progressive increase.

These findings also suggest that reperfusion-induced arrhythmias are not significantly related to the severity of pathomorphological damage to the myocardium during ischemia and reperfusion in the surgical setting. Ischemia is introduced by aortic clamping and cardioplegia administration. The entire myocardium is completely ischemic, and there is no clear border between the ischemic and nonischemic zones during aortic clamping. Reperfusion of the previously ischemic myocardium is also homogeneous. Moreover, complete diastolic arrest of the heart is established by high-potassium cardioplegia and topical cooling throughout aortic clamping. The heart rate during ischemia cannot be a variable influencing the induction of RVF under the condition of an open heart operation.

The other clinical study presented results similar to ours. Lake and colleagues [13] analyzed the determinants of resumption of cardiac electrical activity after cardioplegic arrest in patients who underwent coronary artery bypass grafting. Fifty-two of the 99 patients exhibited spontaneous restoration of electrical activity of the heart. In these patients, plasma potassium and magnesium concentrations were significantly higher, myocardial temperature was significantly lower, and reperfusion time was significantly shorter compared with patients in whom ventricular fibrillation developed on reperfusion and defibrillation occurred spontaneously or with direct-current shock. These results may concur in part with ours, although the duration of aortic occlusion and plasma calcium concentrations did not relate to spontaneous resumption of normal cardiac rhythm in their study.

Lake and associates [13] classified the patients who had spontaneous resumption of cardiac electrical activity but later required electrical defibrillation in the group without ventricular fibrillation. In fact, 77 (78%) of the 99 hearts in their study were defibrillated by several applications of direct-current shock. We defined RVF as any electrical instability developing and requiring electrical defibrillation during the early period of reperfusion. Inhomogeneity of electrical recovery of the previously ischemic myocardium occurs within a few minutes after the initiation of reperfusion, and this condition has been suggested as a main underlying mechanism of RVF [3]. Therefore, any intractable ventricular fibrillation during this early phase of reperfusion should be treated as RVF even if it appears suddenly after resumption of normal cardiac electrical activity.

There have been a number of laboratory studies in which the mechanisms and pharmacological control of reperfusion arrhythmias have been examined. α-Adrenergic receptor activity [6, 7], plasma potassium level [8], heart rate [9], oxygen radical generation [10, 11], and severity of ischemia [12] have been thought to be significant factors influencing production of RVF. Our previous studies using rats also demonstrated that calcium antagonists effectively prevent the occurrence of RVF in in vivo [19] and in vitro [16] preparations. In addition, we have suggested the important role of rate of recovery in extracellular potassium concentration just after initiation of myocardial reperfusion (unpublished data). These basic experimental works, although ischemia was not global, may partly support the results of the present study.

Our recent clinical study [20] found that patients receiving St. Thomas' Hospital cardioplegia, which contains relatively high amounts of calcium, had a higher incidence of RVF compared with patients receiving our low-calcium cardioplegia. Also, the calcium concentration in the reperfusate was significantly higher in the former group. Thus, a series of our experimental and clinical investigations strongly suggests that the occurrence of RVF is largely dependent on cation balance, such as calcium and potassium, during the early phase of reperfusion.

The electrophysiological activity of the myocardium is also thought to be temperature dependent. Lowering temperature causes an increase in action potential duration, which, in turn, suppresses the propagation of the reentry circuit. Cooling also decreases the rate of rise of pacemaker depolarization in Purkinje's fibers, and therefore electrical automaticity may be suppressed. These alterations caused by lowering the temperature can result in an antiarrhythmic action. Conversely, a higher temperature will be arrhythmogenic for the myocardium, probably on reperfusion.

Since Jennings and associates [21] demonstrated acceleration of myocardial injury after abrupt coronary reflow after a period of ischemia, this paradoxical pathological phenomenon has been given much attention by several investigators and has been called "reperfusion injury." The most remarkable finding of reperfusion injury is a rapid accumulation of intracellular calcium ions immediately after the initiation of myocardial reperfusion [22]. Similarly, massive leakage of CK from the previously hypoxic myocardium appears within 5 to 10 minutes of reoxygenation [23]. The time to onset of reperfusion arrhythmias has also been reported to be within seconds or a few minutes of reperfusion [3, 15, 16], as in the present study. Thus, it may be argued that rhythm disturbances induced by reperfusion are strongly associated with or representative of reperfusion injury to the myocardium. If this hypothesis is accepted, studies on reperfusion arrhythmias can be valuable to approach the underlying mechanisms and control of reperfusion injury.

Evaluating the severity of RVF may also be useful to assess the magnitude of myocardial tissue injury induced by reperfusion. In the present study, we demonstrated that ion balance and myocardial temperature during reperfusion are the most important correlates of reperfusion arrhythmias, but the severity of the preceding period of ischemia (the duration of ischemic time) and the extent of postoperative myocardial damage (the amounts of serum CK-MB and myoglobin) did not affect them. It might be suggested that there is a dissociation between electrical abnormalities and pathomorphological changes induced by myocardial reperfusion. Thus, our present study, in which reperfusion was established after hypothermic cardioplegic arrest of the globally ischemic heart during a cardiac operation, may give a clue to verify the nature of reperfusion injury. Under such conditions, postoperative myocardial injury is attributed mainly to the ischemic insult itself, not to additional reperfusion.

The present study suggests that reperfusion-induced arrhythmias appearing after ischemic arrest of the heart with cardioplegia and hypothermia are dependent on ion imbalance and myocardial temperature at the time of reperfusion but not the extent of myocardial tissue damage. Under these conditions, reperfusion injury, if reperfusion arrhythmias are one of the specific aspects of reperfusion injury, may not be attributable to postoperative cardiac dysfunction.

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Penetrating Cardiac Trauma: Management Strategy Based on 129 Surgical Emergencies Over 2 Years

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Between 1986 and 1988, 129 patients with stab wounds to the heart were referred from the emergency room of our institution for a thoracic surgical procedure. Multiple entrance wounds of the heart were present in 12 patients, and through-and-through stab wounds were encountered in another 10. The overall hospital mortality rate was 8.5% (11/129), which includes a 54% mortality rate for the 13 patients undergoing emergency room thoracotomy. These patients were pulseless and unconscious either on arrival (n = 8) or soon thereafter (n = 5). Cardiopulmonary bypass was not used during the primary operation, although 7 patients underwent subsequent intracardiac repair with bypass without hospital mortality. Important aspects of our preoperative management strategy include: (1) aggressive transfusion to improve the central venous pressure/intrapericardial pressure gradient; (2) rapid drainage of the pleural and pericardial spaces to reduce intrapericardial pressure; (3) empirical partial correction of metabolic acidosis with sodium bicarbonate; and (4) emergency operation without unnecessary cardiac imaging. Patients suspected of having penetrating cardiac trauma and cardiac tamponade are best managed by aggressive primary intervention and immediate operation.

(Ann Thorac Surg 1992;53:1006–9)

Surgical repair of penetrating wounds of the heart and great vessels has improved dramatically over the past decades. As recently as the beginning of the 20th century, the management of this catastrophic injury was clearly ineffective, and the outcome for patients with cardiac stab wounds was therefore usually fatal. Medical management was limited to phlebotomy or the sporadic use of pericardiocentesis [1], and surgical intervention had only rarely been attempted [2–4]. In 1896, Paget [5] stated that surgery of the heart had reached the limits set by nature and that no new discovery could overcome the difficulties that wounds of this organ presented. Oddly enough, that same year marked both the unsuccessful attempt by Cappelen [2] to suture a human heart and the successful repair by Rehn [3] of a cardiac wound resulting from a stab with a kitchen knife. This latter event introduced to the medical world the feasibility of cardiac surgery in general.

The next major advance in the treatment of penetrating cardiac trauma was provided by Blalock and Ravitch [6] in 1943. They advocated the use of emergency pericardiocentesis as initial therapy for cardiac tamponade, and this therapy has continued to play an important role in its management [7–9]. The remainder of this century has seen the steady improvement of outcome with surgical repair of cardiac wounds mainly through improved surgical technique [10–12] and, more recently, through expediting stabilization and immediate surgical intervention [13–17].

During the recent periods of unrest in South Africa, our hospital has seen a marked increase in the number of patients with penetrating cardiac trauma. As a result, our management of these patients has evolved to the point where we currently enjoy very low operative morbidity and mortality, despite the relative inexperience of the surgery and anesthesia residents primarily responsible for treating these patients.

Here we share our management strategy, which is based on a recent 2-year experience with more than 100 surgical emergencies.

Material and Methods

Between June 1986 and May 1988, 129 patients with penetrating cardiac trauma were admitted to the resuscitation unit at our institution. All of the injuries resulted from stab wounds. Eight patients had unrecordable vital signs on arrival (ie, unconscious with absent pulse and blood pressure), although the emergency ambulance personnel reported that vital signs were obtainable just before arrival. These patients were considered "possibly salvageable" and underwent emergency thoracotomy in the resuscitation unit. An additional 5 patients lost their vital signs soon after arrival in the emergency room and were categorized as "critically unstable." They also underwent immediate thoracotomy. The charts of all patients were reviewed in August 1988.

The remaining patients (n = 116) all had penetrating wounds of the chest or upper abdomen (target area) associated with low cardiac output and other evidence of

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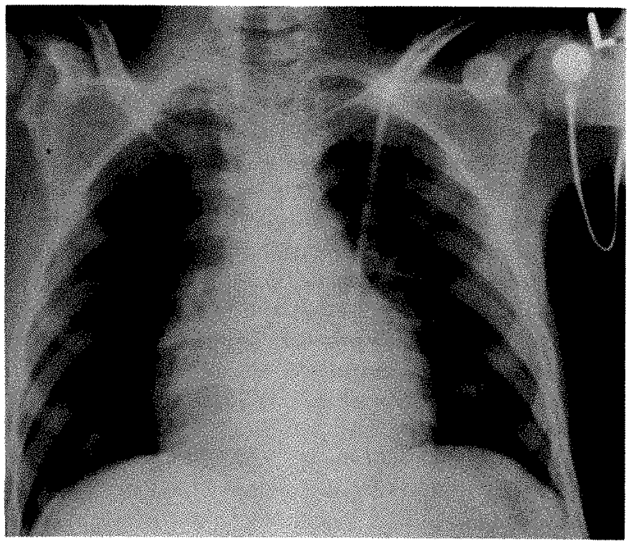

Fig 1. Preoperative chest roentgenogram of a 9-year-old boy stabbed in the right ventricle with a knitting needle.

cardiac tamponade (ie, distended neck veins and pulsus paradoxus). This clinical suspicion of cardiac trauma resulted in an emergency operation in every instance. Diagnostic studies other than a chest roentgenogram were rarely performed.

The mean age of the 129 patients was 24 years (range, 9 to 48 years). There were 120 male and 9 female patients. Most of the injuries resulted from intraracial violence, and there were no self-inflicted wounds. The youngest patient was a 9-year-old boy who was accidentally stabbed with a knitting needle in a school classroom (Fig 1).

Chronological Distribution of Trauma

The incidence of cardiac trauma according to the time of day that emergency operation commenced, the day of the week, and the month in which the patients were seen has not changed significantly in our experience over the past decade [14]. Seventy-three percent of patients were seen during the summer months of September to February. Eighty-four percent of the injuries occurred on weekends, with 61% of the operations commencing between 8:00 PM and 4:00 AM. Volume during these periods was often heavy, with one instance in which 4 patients were seen in 1 day.

Management Strategy

The strategy that evolved for the resuscitative management of our patients can be summarized as follows:

- Increase Central Venous Pressure (CVP)
    - Transfuse aggressively
    - Maintain venous tone
    - Avoid analgesia, muscle relaxants, sedatives
- Reduce Intrapericardial Pressure (IPP)
    - Drain pleural collections of blood and air
    - Perform pericardiocentesis
    - Avoid positive-pressure ventilation
    - Perform emergency room thoracotomy
- Partially Correct Metabolic Acidosis
    - Infuse ±3 mEq/kg of sodium bicarbonate

With the arrival of the patient in the emergency room, large-bore central venous access, usually through the subclavian vein, was rapidly achieved and crystalloid transfusion, commenced. While spontaneous respiration occurred, oxygen was administered through a face mask, and blood was drawn for arterial blood gas and electrolyte analyses as well as blood group cross-matching. Priorities then focused on (1) identifying and treating causes of the increase in IPP (eg, pneumothorax, hemothorax, or hemopericardium) while avoiding, if possible, maneuvers such as positive-pressure ventilation that might further increase IPP; (2) increasing CVP by aggressive transfusion and avoiding treatment options that might reduce venous tone and therefore CVP (eg, analgesia, muscle relaxants, and sedatives) until the operation began, and (3) empirically partially correcting the inevitable severe metabolic acidosis by infusing sodium bicarbonate, 3 mEq/kg of estimated patient body mass. Although this is substantially more than generally recommended, the dose has been shown to half correct the metabolic acidosis in this situation (unpublished data).

"Crash intubation" and hand ventilation, emergency pericardiocentesis, and emergency room anterolateral left thoracotomy for decompression of the tamponade and control of the bleeding were used for patients classified as "possibly salvageable" or "critically unstable." Definitive repair and closure of the cardiac wound was done once the patient had been transferred to the operating room.

For patients in stable enough condition to be transferred to the operating room, the surgeon and scrub nurse were scrubbed and ready to drape the patient before the anesthetist started the induction of anesthesia. Because most of our patients had eaten recently, ketamine hydrochloride and succinylcholine chloride were used for the induction, or the patient was intubated under local anesthesia and allowed to breathe spontaneously until the operation commenced.

The skin incision usually started while the patient was being intubated. The chest was opened through a median sternotomy (84% of patients), although an anterolateral thoracotomy was occasionally used (16%) either for expediency or because of the surgeon's preference. With the decompression of the pericardium, immediate improvement in the hemodynamic status of the patient usually occurred. At this point, the cardiac wound was controlled by manual compression, the rapid transfusion of fluids was discontinued, and the heart was allowed to recover. Only then were the cardiac lacerations repaired. Atrial and aortic wounds were preferably sutured over a partial-occluding vascular clamp, whereas ventricular and pulmonary artery wounds were repaired de novo using a 3-0 polypropylene suture mounted on a large needle. The suture techniques have been well described elsewhere [18].

The cardiopulmonary bypass perfusionists were not routinely notified, and in this experience, cardiopulmo-

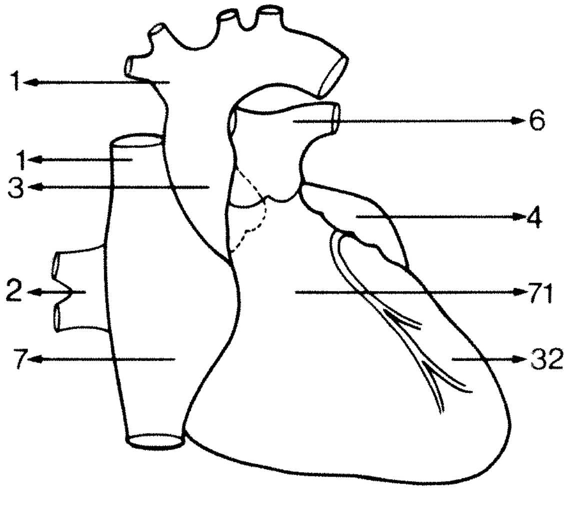

Fig 2. Anatomical distribution of the major cardiac entrance wounds, all of which resulted from stabbings, in 129 patients (2 patients had negative explorations).

nary bypass was not needed in the primary repair. The patients were primarily managed by residents in thoracic surgery and anesthesia, many of whom were early in their residency training programs. Those patients who required definitive intracardiac repair (n = 7) usually underwent the operation during the same admission. However, the timing was based on their clinical status.

Results

The distribution of the major cardiac entrance wounds is depicted in Figure 2. More than half the wounds involved the right ventricle (n = 71). The left ventricle was penetrated in slightly less than 25% (n = 32), and the remaining 24 major entrance wounds were distributed between the atrial chambers and cardiac veins. In 2 patients, no cardiac wound was identified at operation although the pericardium had been breached and contained a moderate amount of blood.

Complex stab wounds of the heart occurred in 17% of patients (22/129). Of these, multiple entrance wounds were present in 12 patients and through-and-through wounds, in 10 patients. These wounds reflect the determined aggression of the assailants in inflicting their assaults. The weapon in these cases generally entered the inlet portion of the right ventricle, traversed the interventricular septum, and exited the heart through the diaphragmatic surface of the left ventricle, sometimes penetrating the diaphragm and liver as well. Other examples of through-and-through wounds dealt with during the primary repair included left ventricle–left ventricle wounds and wounds entering the anterior wall of the ascending aorta and exiting through the posterior wall of the right pulmonary artery.

Intracardiac lesions requiring subsequent definitive surgical repair occurred in 7 patients (5.4%). Three had an isolated ventricular septal defect, 2 had a ventricular septal defect and laceration of the anterior mitral valve leaflet, and 2 had a ventricular septal defect and traumatic aortic–right ventricular fistula with associated laceration of the right cusp of the aortic valve. All 7 patients underwent repair with cardiopulmonary bypass without hospital mortality.

The overall mortality rate for the patient population was 8.5% (11/129). The mortality rate among patients whose condition was stable enough to allow surgical intervention in the operating room was 3.4% (4/116). In contradistinction to this, 7 (54%) of the 13 patients needing emergency room thoracotomy died, 1 (20%) of 5 of those categorized as "critically unstable" (ie, who became unconscious and pulseless in the emergency room) and 6 (75%) of 8 of those categorized as "possibly salvageable" (ie, who arrived at the hospital without recordable vital signs).

The causes of death for the 5 patients who arrived at the hospital without cardiac arrest were coronary embolism in 2, intractable arrhythmias in 2, and major cerebral embolism in 1. Residual neurological deficit (2 patients), wound infection (2 patients), and anterior Q-wave infarction (1 patient) represented an overall major morbidity of 3.9%. The average hospital stay was 4.6 days.

Comment

The pericardial space normally can accommodate an acute accumulation of about 80 to 100 mL of fluid without greatly affecting the physiologically negative IPP [19]. Only small additional amounts of fluid within the pericardial sac are necessary to greatly increase the IPP. In penetrating cardiac trauma, hemopericardium develops under pressure, and the body must necessarily compensate to maintain a CVP sufficiently higher than the IPP to effect ventricular filling and sustain cardiac output (Fig 3) [14, 20–22]. The major concern in the management of cardiac stab wounds is therefore the maintenance of the CVP/IPP gradient. Cardiac tamponade occurs as these

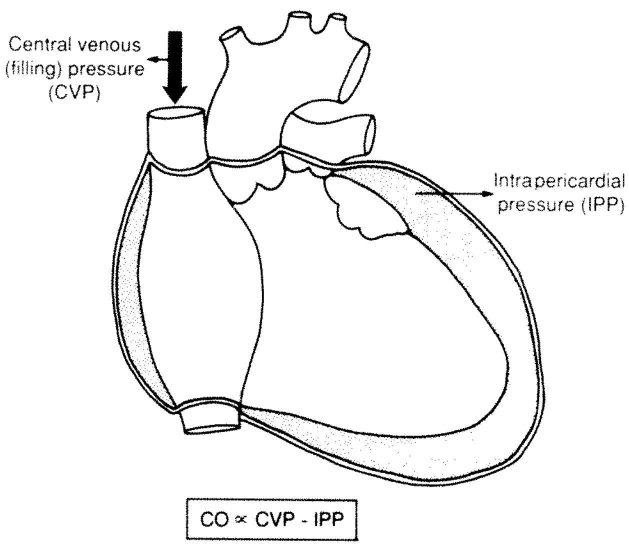

Fig 3. Pathophysiology of cardiac tamponade. (CO = cardiac output.)

pressures equalize and the gradient disappears. Hypovolemia and vasodilatation aggravate the tamponade by decreasing the CVP, whereas intrapericardial blood and increased intrathoracic pressure (eg, pneumothorax or hemothorax) increase the IPP.

Iatrogenic contributions to a diminished CVP/IPP gradient include use of analgesics and muscle relaxants, which decrease venous tone, and use of positive-pressure ventilation, which increases IPP. If at all possible, these should be avoided until the surgical team is ready to decompress the pericardium. Although emergency pericardiocentesis may be lifesaving in this regard, the usually large amount of blood clot in the anterior pericardium, which often cannot be aspirated, makes the success of pericardiocentesis unpredictable. Currently, we use it only in the emergency situation.

By adhering to these principles, we have found that most cardiac stab wounds can be managed quite effectively for short periods, allowing emergent transfer of the patient to the operating room. The mortality rate of 3.4% for our subgroup having emergency operation in the operating room compares very favorably with that in similar reports, which generally exceeds 10% [11, 15–17, 23]. Our results with the subgroup requiring emergency room thoracotomy (54% mortality rate) also compare favorably with the mortality rate in similar reports, which ranges from almost 100% [24, 25] to 26% [17].

Preoperative diagnostic imaging with ultrasound [26] in the emergency situation has been time-consuming and ineffective as a diagnostic tool in our experience. Critically ill patients in cardiorespiratory distress usually are not cooperative enough for an adequate echocardiographic examination. We have relied on clinical judgment and encourage a low threshold for emergency exploration in patients suspected of having a penetrating wound to the heart. The low rate of negative explorations (1.5%) justifies this policy in our opinion. However, high-velocity cardiac wounds probably demand a more accurate diagnosis, and better intraoperative imaging with transesophageal access would be helpful in this regard. We did not have this technology available during the time under review.

The presentation of patients with penetrating cardiac trauma and the rapidity with which decompensation can occur in these patients are intimidating. However, by adhering to certain fundamental principles of aggressive primary intervention and immediate operation, we have found that such patients can be managed quite effectively by relatively inexperienced surgery and anesthesia residents. It may be that exporting an effective management strategy to more peripheral or rural hospitals, rather than relying on tertiary centers such as our own, will be the next major step in improving the management of patients with penetrating cardiac trauma.

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Push-Through Intubation: Effective Palliation in 409 Patients With Cancer of the Esophagus and Cardia

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Between 1980 and 1989, 355 patients with cancer of the esophagus and 54 with cancer of the cardia underwent push-through intubation because of advanced tumor stage or medical contraindications to tumor resection. In 36 other patients (8.1%), the attempt at transtumoral intubation failed. The hospital mortality rate after intubation was 3.4%. The following complications were observed: hemorrhage in 2.0% of the patients, esophageal perforation in 4.9%, tube dislodgment in 12.7%, and tube obstruction in 4.4%. Early resumption of semisolid oral feeding was possible in 80% of the discharged patients. The actuarial 1-year survival rate was 7.7% and the median survival, 3.9 months. In conclusion, push-through intubation represents a valid therapeutic choice, which is indicated mainly for patients with a long, infiltrating, and circumferential stricture of the thoracic esophagus or cardia that is inoperable and for patients with an esophagorespiratory or esophagomediastinal fistula.

(Ann Thorac Surg 1992;53:1010–4)

Surgical resection is generally considered the treatment of choice for esophageal and cardiac cancers. When resection can be performed with curative intent, it gives the best results for dysphagia and is the only hope of cure [1, 2]. However, only 60% of the patients with cancer of the esophagus or cardia are eligible for radical operative intervention [3]. In the other 40%, the most realistic therapeutic goal is simply palliation of dysphagia and aspiration pneumonia.

The ideal type of palliation should guarantee early resumption of oral feeding at the expense of minimal morbidity, even for patients in poor general condition, and should not require long or repeat hospital admissions. The most common palliative treatments are performed endoscopically: dilation, neodymium:yttrium-aluminum garnet laser therapy, transtumoral push-through intubation, and BICAP electrocoagulation [4–8].

The aim of the present study was to evaluate critically the results obtained with 409 push-through intubations and 36 failed attempts at intubation, which were carried out in 445 consecutive patients with inoperable cancer of the esophagus or gastric cardia.

Material and Methods

Patient Population

Between 1980 and 1989, 1,698 patients with cancer of the esophagus and 400 with adenocarcinoma of the gastric cardia were seen. Before a decision on treatment was made, all patients were examined by means of upper gastrointestinal tract barium or Gastrografin (diatrizoate meglumine and diatrizoate sodium solution) swallow, chest roentgenogram, electrocardiogram, endoscopy plus biopsy, and computed tomographic scan of the chest and upper abdomen. Bronchoscopy and ultrasonography of the neck were performed in patients with a tumor of the retrotracheal esophagus. Magnetic resonance imaging has been used recently whenever the findings of bronchoscopy and computed tomographic scanning were discrepant and to probe the question of aortic infiltration. Endoscopic ultrasonography has been used since 1988 for tumors pervious to the endoscope. Laparoscopy and echography of the liver were performed in patients with a tumor of the lower esophagus or cardia and whenever liver cirrhosis was suspected clinically. Pulmonary function tests were performed in patients with a potentially resectable tumor.

Surgical resection was the treatment of choice. Of the 2,098 patients, 825 underwent curative resection; 294, palliative resection; 750, surgical or endoscopic palliative procedures without resection; and 229, medical treatment only.

The current indications for intubation are infiltrating or ulcerated, circumferential strictures more than 4 cm long of the thoracic esophagus and cardia and tumors with mediastinal or tracheobronchial fistula formation. Up to 1985, when the neodymium:yttrium-aluminum garnet laser equipment became available to us, stiff strictures caused by protruding tumors and tumors shorter than 4 cm were also treated by intubation. Tumors located less than 3 cm distal to the upper esophageal sphincter have

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been considered a contraindication to intubation, as the tube may cause a foreign-body sensation in the throat and may cause a sudden obstruction of the airway if it dislodges proximally.

Overall, 409 patients underwent transtumoral push-through intubation. In 36 additional patients, the attempt at endoscopic intubation failed, a failure rate of 8.1%.

Esophageal intubation was the first form of treatment in 373 patients. In 36 others, it was performed during follow-up after various types of treatment: neodynium: yttrium-aluminum garnet laser therapy in 16, intratumoral injection of polidocanol in 2, exploratory cervicotomy in 1, dilation in 1, pull-through intubation in 1 (dislocated tube), supportive medical treatment of nonstenosing cancers in 6, and esophagectomy plus esophagogastrostomy (neoplastic recurrence) in 9.

The mean age of the 373 patients who underwent elective intubation was 65.9 years (range, 26 to 89 years); 116 patients (31.1%) were 71 years old or older. The male to female ratio was 4:3. The tumor was located in the cervical esophagus in 2 patients (0.5%) who had already undergone laryngectomy, the upper thoracic esophagus in 87 (23.3%), the middle thoracic esophagus in 173 (46.4%), the lower thoracic esophagus in 69 (18.5%), and the cardia in 42 (11.3%).

Of the 331 patients with esophageal cancer, 155 (46.8%) were considered to have inoperable disease because of poor general condition, age, or severe concomitant diseases and 138 (41.7%), because of advanced tumor stage. In the latter group, 34 and 19 had an esophagorespiratory or esophagomediastinal fistula, respectively. In 38 other patients (11.5%), the tumor appeared to be inextirpable at operation and the prosthesis was inserted endoscopically during exploratory thoracotomy in 35, exploratory laparotomy in 2, and exploratory cervicotomy in 1. Fourteen patients were also treated with radiotherapy, 38 with chemotherapy, and 6 with chemoradiotherapy.

Of the 42 patients with cardiac cancer, 21 (50%) were considered to have inoperable disease because of medical contraindications and 20 (47.6%), because of advanced tumor stage. In 1 additional patient, (2.4%) the prosthesis was positioned endoscopically during exploratory laparotomy.

Technique

Endoscopic push-through intubation was performed under oropharyngeal local anesthesia, induced with intravenous administration of hydrochloride buprenorphine, and light general sedation, induced with intravenous administration of flunitrazepam. A pediatric endoscope with a caliber of 7.8 mm was the ideal instrument, as it can pass through the stricture and allows a thorough evaluation of the lesion [9]. Figure 1 shows the technical details of intubation.

The following preliminary steps were considered mandatory to make the intubation safe: positioning a guidewire well inside the stomach or into the duodenum and performing progressive dilations of the stricture. We generally used Savary-Gilliard dilators [10]. Only in the case of very stiff strictures did we use Eder-Puestow dilators. Recently, through-the-scope balloon pneumatic dilators were used during the initial phases of dilation of particularly narrow or stiff neoplasms [11] and in the case of neoplastic anastomotic strictures after esophagoplasty. Fluoroscopic control was indicated when it was impossible to pass the guidewire under direct vision and when the axis of the stricture was particularly angular. In our experience, preliminary dilations up to a caliber of 14 or 15 mm were necessary to insert a standard-caliber tube, and dilations up to 12 mm were sufficient for pediatric prostheses.

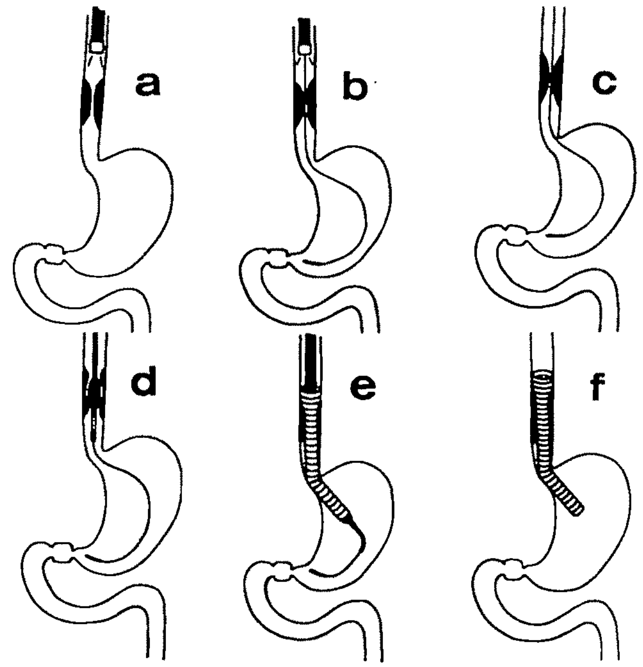

Fig 1. Technique of push-through intubation: (a) endoscopic check of the tumor; (b) passage of guidewire through the stricture; (c) withdrawal of the scope with guidewire left well inside the stomach; (d) dilation of the stricture; (e) positioning of the endoesophageal tube by means of the introducer; and (f) withdrawal of the introducer with the tube left through the stricture.

Nottingham and Dumon-Gilliard [10] introducers were used. The Nottingham device is particularly useful when treating strictures of the thoracic esophagus, whereas the Dumon-Gilliard introducer is indicated for strictures at the cardia, even in the presence of an angular esophagogastric axis.

We have mostly used Celestin tubes (Fig 2) because they are easier to manage and less traumatizing [12]. These tubes are available in pediatric (internal diameter, 8 to 9 mm) and standard sizes (internal diameter, 11.5 to 12 mm) and can be provided with an antidislocation flange at the distal end. Less frequently we have used Atkinson and Wilson-Cook tubes (see Fig 2). These tubes can also be provided with a cuff, which is useful to exclude esophagomediastinal or esophagorespiratory fistulas [13].

The tube should be at least 3 cm longer than the neoplastic stricture both proximally and distally to pre-

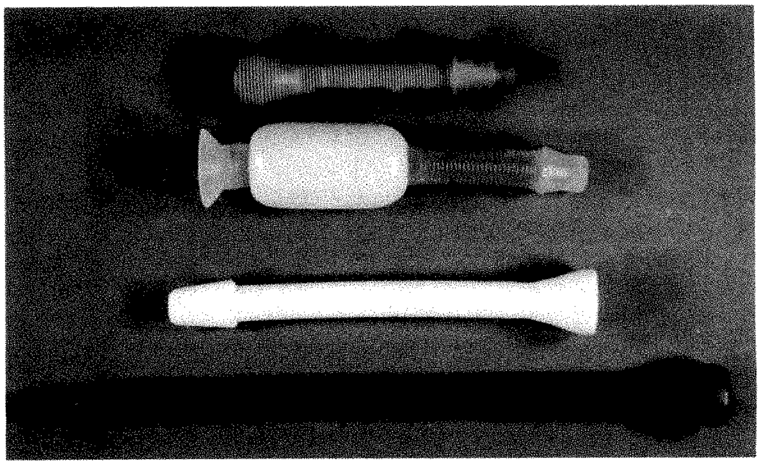

Fig 2. Different types of esophageal tubes: (from top to bottom) Celestin tube with antidislocation flange, cuffed Wilson-Cook tube, Atkinson tube, and Celestin tube.

vent obstruction resulting from neoplastic overgrowth. When the tumor involves the upper and middle thoracic esophagus, it is always advisable to position the distal end of the tube above the lower esophageal sphincter to prevent esophagogastric reflux.

After esophageal intubation, a nasogastric tube was inserted, and a Gastrografin swallow was performed within 24 hours to check the positioning of the tube and to rule out the possibility of a leak. The nasogastric tube was withdrawn afterward, and the patient was allowed a semisolid diet.

Results

Between 1980 and 1989, 409 patients with cancer of the esophagus or cardia underwent intubation as a first choice procedure or during follow-up after other types of treatment. In 36 additional patients, the attempt at intubation failed because it was impossible to pass the guidewire or the introducer through a stricture that was either too tight or very angular. Hence, the failure rate was 8.1%.

The hospital mortality rate for the 409 patients who underwent esophageal intubation was 3.4% (14/409); it was 5.6% (2/36) for the patients who had a failed attempt at intubation. The causes of death were as follows: perforation, 6 of 409 patients and 1 of 36; hemorrhage, 2 and 0, respectively; pulmonary failure, 2 and 1, respectively; bronchopneumonia, 1 and 0, respectively; and cardiac failure, 3 and 0, respectively.

Overall, 26 perforations were observed: 20 (4.9%) after 409 intubations and six (16.7%) after 36 failed attempts. Six patients and 1 patient, respectively, died of this complication. The management of perforations and the results are summarized in Table 1. A conservative therapeutic approach was successful in most patients with a small leak and in the absence of sepsis. Four palliative esophagectomies and two bypass operations were performed on an emergency basis because of large perforations with pleural effusion.

Fifty-two patients (12.7%) had tube dislocation. Management of this complication was as follows: endoscopic removal of the tube and reintubation (same caliber), 12 patients; endoscopic removal of the tube and reintubation (larger caliber), 12; endoscopic removal of the tube, 16; surgical removal of tube and alimentary gastrostomy, 3; endoscopic removal of the tube and surgical reintubation, 4; bypass (esophageal perforation subsequent to endoscopic removal of the tube), 1 patient; and no treatment, 4.

Table 1. Management and Outcome of Perforations Associated with Successful and Unsuccessful Intubation

	No. of Patients		Deaths	
Treatment	Successful	Unsuccessful	Successful	Unsuccessful
Conservative management	11	0	0	0
Conservative management + gastrostomy	0	1	0	0
Endoscopic tube repositioning	1	1	0	0
Endoscopic tube removal	2	0	1	0
Surgical tube removal + reintubation	1	0	1	0
Endoscopic tube removal + drainage + gastrostomy	2	0	2	0
Suture + drainage + gastrostomy	0	1	0	0
Esophagectomy + esophagogastrostomy	1	3	1	1
Bypass operation	2	0	1	0
Total	20	6	6	1

Tube obstruction by tumoral overgrowth or food impaction was observed in 18 patients (4.4%). The obstruction was removed endoscopically in 15 patients. In 1 patient, the tube was repositioned endoscopically; in another, it was removed and repositioned surgically; and in 1, it was left in place and a feeding jejunostomy was performed.

Of the 8 patients (2.0%) with hemorrhage, 6 had moderate bleeding with melena during the days after intubation; they were treated conservatively. Two patients died of massive bleeding on days 8 and 15 after intubation; postmortem examination of the first patient showed cancer erosion into the aorta.

In the presence of a neoplastic esophagorespiratory fistula, the endoesophageal tube excluded the fistula successfully and allowed resumption of oral feeding in 25 (73.5%) of the 34 patients. In 9 patients (26.5%) the fistula was not excluded, and the persisting symptoms required nasogastric tube or gastrostomy feeding.

Miscellaneous complications were observed in 14 patients: thoracic pain, which was not relieved by analgesics and necessitated tube removal, in 1 patient; respiratory failure in 3 patients, which was lethal in 2; bronchopneumonia in 3, which was lethal in 1; cardiac failure in 3, which was lethal in all 3; pulmonary embolus in 1; pleural empyema in 1 patient who had undergone intubation during exploratory thoracotomy; acute ischemia of the left leg in 1 patient who required axillofemoral bypass; and reflux-induced peptic stricture above the prosthesis necessitating tube removal in 1 patient.

All patients without complications resumed oral feeding on the day after the procedure. The average duration of hospital stay was 4 days. The discharged patients spent the rest of their lives at home and were followed up on an outpatient basis every 30 to 60 days whenever possible. Twenty percent were able to enjoy a virtually normal diet, 60% could swallow semisolid food, and 20% had troublesome dysphagia and were forced to survive on liquids only, nasogastric tube feeding, or supplementary intravenous nourishment.

The actuarial 6-month, 1-year, and 2-year survival rates were 36.6%, 7.7%, and 1.4% (4 patients), respectively. No patient reached the 3-year interval. The median survival was 3.9 months.

Comment

The prognosis for patients with inoperable esophageal or cardiac cancer is death within a few months. It is therefore important that restoration of swallowing be achieved quickly, simply, and safely [14]. However, the optimum method of restoring the ability to swallow is still controversial [8]. Palliative esophagectomy, if performed on unselected patients, has high morbidity and mortality rates [14] and does not prolong survival in comparison with other less traumatizing palliative procedures [15]. Bypass operations have even higher hospital morbidity and mortality rates [16], and therefore their indication should be limited to patients with an esophagorespiratory fistula who are still in satisfactory general condition [17].

Radiation therapy has not proved to be effective in the palliation of esophageal cancer. After radical irradiation, 70% of patients have early recurrence of dysphagia [18], and only 20% to 30% of patients who undergo palliative radiotherapy have temporary improvement in dysphagia [19]. Encouraging results have recently been reported with polychemotherapy and combined chemotherapy and radiotherapy [20–22], but the toxicity of these regimens is not negligible.

Pull-through intubation is obsolete because the morbidity and mortality rates are great [23, 24]. Nasogastric tube feeding and alimentary gastrostomy should be reserved as the very last resort.

There are several possibilities for palliating dysphagia endoscopically. Esophageal dilation leads to only short relief of dysphagia, and repeat dilations are required. Esophageal intubation allows only semisolid feeding [8], and it is not advisable for strictures of the cervical esophagus [7]. Laser therapy requires expensive equipment, entails frequent treatment sessions, and is indicated for exophytic tumors shorter than 5 cm, even if they are located in the proximal esophagus [7]; tracheoesophageal fistulas are an absolute contraindication. Overall, both endoscopic intubation and laser therapy provide effective palliation and have comparable morbidity and mortality rates [25, 26]. The BICAP tumor probe [27] is a safe, effective, and inexpensive form of treatment, especially useful for long, circumferential, and submucosal infiltrating strictures, even if they are located in the low cervical esophagus. Intratumoral injection of necrotizing or antineoplastic substances (polidocanol, 98% ethanol, bleomycin sulfate, or 5-fluorouracil) may be effective.

The type of palliative procedure should be chosen case by case after evaluating the general condition of each patient and the characteristics of the tumor. Also patient compliance and the presence of possible geographic problems should be kept in mind when a type of palliation requiring repeat treatment sessions is under consideration.

In our opinion, palliative endoscopic intubation is the first treatment of choice for patients with inoperable disease who have severe dysphagia because of a long (more than 4 cm), infiltrating, and circumferential cancer of the thoracic esophagus. Extrinsic esophageal compression represents another indication. Furthermore, intubation is the only therapeutic choice for patients with an esophagorespiratory or esophagomediastinal fistula, and for patients who have previously been treated unsuccessfully with laser therapy or endoscopic dilation or who have a recurrent neoplastic stricture after esophagectomy. Finally, esophageal intubation can be carried out during an exploratory operation when the tumor cannot be extirpated.

Success and complication rates of push-through intubation probably depend also on the experience and technical expertise of the operator and on the selection of patients [28]. The failures of push-through intubation were mainly due to the impossibility to pass the guidewire or introducer through a very tight or angular stricture; this was most frequently observed in malignancies at the esophagogastric junction (12/66 or 18.2%) in comparison with esophageal tumors (24/359 or 6.7%). The difference was significant (χ^2 test, $p < 0.005$).

The perforation rate was comparable in patients with esophageal and cardiac cancer: 5.9% and 6.2%, respectively. To reduce the likelihood of perforation, intubation should always be preceded by careful and progressive dilation, even if more sessions are therefore necessary.

Reflux through the tube was not a real problem: only 1 patient required tube removal to treat a peptic stricture above the prosthesis. Reflux was usually prevented by advising patients to go to bed not earlier than 1 hour after meals, to sleep with two pillows under the head, and to take gastric antisecretory medications.

Bolus obstruction of the tube was prevented in the majority of patients by following a semisolid diet and drinking carbonated water or beverages during and after meals. Only in a very few patients did bolus impaction necessitate endoscopic relief of obstruction. Obstruction caused by neoplastic overgrowth could be managed endoscopically by laser therapy or BICAP probe.

Most patients can resume oral feeding on the first day after intubation. The palliation of dysphagia is often satisfactory and long-lasting.

In conclusion, the type of palliation for inoperable esophageal and cardiac cancers has to be chosen case by case on the basis of the characteristics of the tumor and the general condition of the patient. Push-through intubation represents a valid therapeutic choice in patients with a long, infiltrating, and circumferential stricture of the thoracic esophagus or cardia and in patients with an esophagorespiratory or esophagomediastinal fistula.

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Long-Term Results After Tetracycline Pleurodesis in Spontaneous Pneumothorax

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From 1979 to 1988 483 patients were admitted with primary spontaneous pneumothorax. All patients underwent thoracoscopy to identify the cause of pneumothorax. Chemical pleurodesis with instillation of tetracycline was performed if cysts less than 2 cm in diameter were found. If larger cysts were identified the patient underwent thoracotomy. In 93 patients with cysts larger than 2 cm the recurrence rate after thoracotomy was 4%. In 390 patients treated with intrapleural instillation of tetracycline, the recurrence rate was 16%. Fifty percent of the recurrences occurred within 30 days. The cause of recurrence in 42 patients (69%) was cysts missed at the initial thoracoscopy. This study has demonstrated that thoracoscopy is a reliable and safe method for selection of patients for chemical pleurodesis. It is, however, necessary that the thoracoscopy is meticulous to avoid recurrence from missed cysts.

(Ann Thorac Surg 1992;53:1015–7)

Treatment of spontaneous pneumothorax has been a matter of debate for several decades. Expectation or pleural drainage has been widely used as initial treatment. In this way the symptoms are cured, but the cause of the disease remains. This is manifested by the high recurrence rate of up to 60% after tube drainage [1]. A recurrence rate of that magnitude seems unacceptably high, especially because recurrence may have a fatal outcome [2].

Our policy has been to identify the cause of spontaneous pneumothorax by thoracoscopy. As a consequence, the patients underwent either chemical pleurodesis or immediate thoracotomy with subsegmental pulmonary resection and mechanical pleurodesis with pleural abrasion.

The purpose of the present study was to determine the recurrence rate after treatment of spontaneous pneumothorax with intrapleural instillation of tetracycline and to identify the cause of recurrence after this treatment.

Material and Methods

The study comprises 483 patients admitted with spontaneous pneumothorax during 1979 to 1988. The median age was 35 years (range, 18 to 75 years). There were 319 men (66%) and 164 women (34%). Excluded from the study were patients with chronic pulmonary disease or heart failure.

As initial treatment all patients had a pleural tube placed through the fourth intercostal space. All patients underwent thoracoscopy with general anesthesia. If the thoracoscopy demonstrated cysts with a diameter less than 2 cm, tiny blebs, or a normal lung surface, 1 g of tetracycline dissolved in 10 mL of saline solution was instilled into the pleural cavity. The tetracycline was instilled through a ureteral catheter introduced through the thoracoscope to obtain an equal distribution. If the thoracoscopy revealed cysts larger than 2 cm in diameter, subsegmentary resection and mechanical pleurodesis was performed.

The record of each patient was reviewed with regard to age, sex, primary treatment of pneumothorax, recurrence of pneumothorax, thoracoscopic findings, and treatment. The follow-up was complete in 93% of the patients. The median follow-up was 43 months for patients given tetracycline and 34 months for patients treated with thoracotomy.

Results

In 93 patients thoracoscopy indicated immediate thoracotomy with subsegmental resection of cysts. Four patients (4%) had recurrence of pneumothorax within 30 days. One patient underwent repeat thoracotomy with resection of a ruptured cyst. The remaining 3 patients were treated with pleural drainage. No subsequent recurrence has been observed in these patients. In 390 patients tetracycline was instilled. The total number of recurrences was 61 (16%). Fifty percent occurred within 30 days and 82% within 1 year. No recurrences were observed after 5 years.

The cause of recurrence was air leakage from cysts missed at thoracoscopy in 69% of the patients. In 10 patients (16%) the cause of recurrence remained unknown as neither thoracoscopy nor thoracotomy was performed (Table 1).

The treatment of recurrence after previous instillation of tetracycline was thoracotomy with subsegmental resection of cysts and mechanical pleurodesis in 38 patients (61%) (Fig 1). Thirteen patients (21%) underwent new thoracoscopy with instillation of tetracycline. Four patients had cysts larger than 2 cm at the thoracoscopy but refused thoracotomy. Ten patients (16%) had development of only a small apical pneumothorax that was

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Table 1. Causes of Recurrent Pneumothorax After Treatment With Intrapleural Instillation of Tetracycline

	Cause of Recurrence		
Time of Recurrence	Cysts >2 cm	Cysts <2 cm, Tiny Blebs, or Adherences	Unknown
<30 days	20	5	6
30–90 days	8	1	1
>90 days	14	3	3

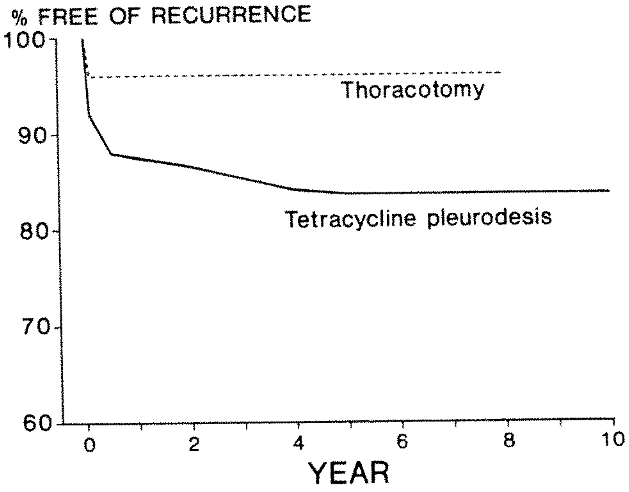

Fig 2. Rate of recurrence of pneumothorax after tetracycline pleurodesis compared with thoracotomy (subsegmentary pulmonary resection and mechanical pleurodesis).

treated with pleural tube drainage. No tertiary recurrences was observed.

After 5 years the cumulated proportion of patients free of recurrence was 84% after thoracoscopy and instillation of tetracycline and 96% for patients treated with subsegmentary resection and mechanical pleurodesis. No further increase in the rate of recurrence was found (Fig 2).

Besides recurrence, postoperative complications developed in 2 patients. Both patients had pleural empyema and were treated with rib resection and tube drainage. The median hospitalization was 5.3 days (range, 3 to 23 days) for patients given tetracycline and 7.2 days (range, 4 to 26 days) for patients who underwent thoracotomy.

Comment

The most common complication of spontaneous pneumothorax is recurrence. Two thirds of the recurrences after tube drainage occur within 2 years after the initial event [3]. Each recurrence increases the risk of another episode of pneumothorax. The recurrence rate after tube drainage only can be as high as 60%, because the cysts or blebs that cause the pneumothorax are still present [1]. The risk of a second pneumothorax after tube drainage is 20% to 80% and 80% to 100% for the third and fourth recurrence [4]. In addition, each subsequent pneumothorax increases the risk of bleeding from vascularized adhesions. The only way to decrease the recurrence rate is to identify the cause of pneumothorax and perform chemical pleurodesis, thoracotomy with subsegmental resection, or mechanical pleurodesis or pleurectomy.

We have routinely used thoracoscopy to assess the cause of pneumothorax. In 93 patients the thoracoscopy revealed cysts larger than 2 cm and the patients underwent immediate thoracotomy. However, in 42 patients we missed cysts larger than 2 cm at thoracoscopy. One explanation is that thoracoscopy is an acute service performed by several doctors during the period of observation and with varying experience. This stresses the importance of careful thoracoscopy, because cysts are located not only at the apex of the lung but occasionally also at the base or in the fissures. Another possibility is that new cysts had developed after the primary treatment with tetracycline.

Surgical treatment of spontaneous pneumothorax has a low recurrence rate. Subsegmental resection in combination with parietal pleurectomy carries the lowest recurrence rate of 0% to 0.5% [5]. We combined subsegmental resection with mechanical pleurodesis and found a recurrence rate of 4%, as reported in similar previous studies [1, 6].

Because a fair proportion of patients with primary spontaneous pneumothorax never have development of recurrence, definitive surgical treatment should not be regarded as the treatment of choice for all patients. Chemical pleurodesis has been shown to be a realistic alternative with a recurrence rate lower than that of tube drainage but higher than that of surgical treatment. Chemical pleurodesis can be achieved by several substances [7]. The current sclerosing agents of choice, as judged from controlled studies, are tetracycline and talc. Tetracycline is an acidic agent that induces a reaction in the mesothelial cells when injected into the pleural space during the thoracoscopic investigation. In recent controlled studies the recurrence rate ranged from 0% to 13% [8–10]. We observed a 16% recurrence rate (61 patients), of which 68% should have been treated initially by operation if a more thorough thoracoscopy had been made. This leaves 19 patients (4.8%) with "pure" recurrence.

In several instances of recurrence after tetracycline pleurodesis we found no or few intrapleural adherences at the subsequent thoracoscopy or thoracotomy. This is most likely due to the fact that the instilled tetracycline

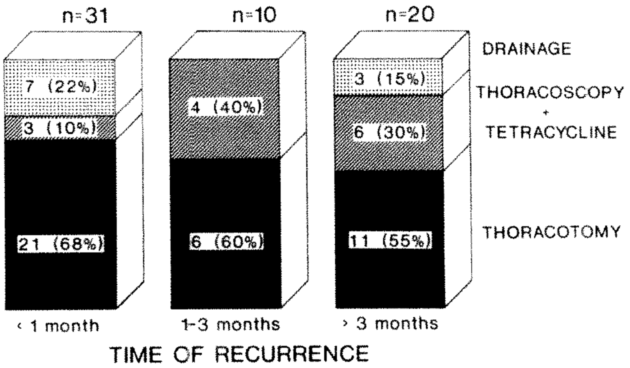

Fig 1. Treatment of recurrence of pneumothorax after previous tetracycline pleurodesis. Fifty percent of the recurrences occurred within the first month after pleurodesis.

had been drained by the pleural tube shortly after instillation, as we do not clamp the tube because of risk of tension pneumothorax. To avoid this, the tube can be elevated 40 to 60 cm above the chest as an inverted U loop, which will trap the tetracycline but allows air under pressure to pass. This procedure has shown to be effective even in patients with persistent air leakage [11].

This study has shown that thoracoscopy is a reliable procedure to identify the cause of pneumothorax and to select patients for chemical pleurodesis or thoracotomy. It is important that the thoracoscopy is carried out in a thorough and careful manner to prevent recurrence from missed cysts on the lung.

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Influence of Alprostadil on Pulmonary Dysfunction After a Cardiac Operation

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To test the effects of alprostadil on pulmonary dysfunction after cardiac operations, we studied 24 male patients undergoing aortocoronary bypass. Twelve were given an intravenous infusion of alprostadil (synthetic prostaglandin E_1), 20 ng · kg^{-1} · min^{-1}, in a double-blind manner during operation; the other 12 were controls. Duration of artificial respirator use and frequent blood gas analyses were used to assess postoperative pulmonary function. Use of the artificial respirator postoperatively was significantly lower in the prostaglandin group (mean time, 5.25 ± 1.81 hours) compared with the controls (mean time, 8.34 ± 4.35 hours) ($p = 0.047$). The proportion of patients with hypercapnia and with hypoxia determined every 4 hours for the first 24 hours after extubation was significantly lower in the prostaglandin group compared with the controls ($p < 0.0001$). These results indicate that synthetic prostaglandin E_1 may play a role in protecting lung tissue during extracorporeal circulation.

(Ann Thorac Surg 1992;53:1018–22)

Despite the recent improvement in the technology of extracorporeal circulation (ECC), pulmonary dysfunction after cardiac surgical procedures is still considered a major complication in some cases, especially if the ECC time exceeds 1 hour [1, 2]. Prolonged treatment with oxygen (O_2) therapy is often mandatory to control hypoxia and hypercapnia, and use of the artificial respirator may exceed the normal limits. Mechanical obstruction of the pulmonary microcirculation by aggregates of platelets, leukocytes, and erythrocytes is considered to be a major factor leading to less effective oxygenation and to increased risk of pulmonary insufficiency after cardiac operations [2]. Pulmonary intravascular leukocyte aggregation and sequestration is particularly important in this context because the lysosomal degeneration that takes place in these cells leads to release of proteolytic enzymes with subsequent destruction of the surrounding structures [2, 3]. From the point of view of blood rheology, pulmonary dysfunction has been shown to be significantly associated with disturbed red and white cell filterability after cardiac operation [4]. Reduced blood rheology may contribute to the precipitation of lung injury by affecting the pulmonary microcirculation [2, 4].

Methylprednisolone has been considered the drug of choice to prevent leukocyte aggregation and stabilize lysosomes [5]. However, more recently, the beneficial effect of prostaglandin E_1 (PGE_1) on pulmonary intravascular leukocyte aggregation during ECC has been described as superior [2]. Recent reports [6] have also shown that PGE_1 protects red cell filterability during ECC for cardiac operations. The aim of this study was to investigate the effects of infusion of alprostadil (synthetic PGE_1) (The Upjohn Company, Kalamazoo, MI) during cardiac surgical procedures with ECC on postoperative pulmonary dysfunction using duration of artificial respirator support and frequent blood gas analyses after extubation as variables for the assessment of lung injury.

Material and Methods

Twenty-four male patients ranging in age from 33 to 70 years undergoing coronary artery bypass grafting with the use of ECC were prospectively studied (Table 1). Patients with known poor left ventricular function, diabetes with severe peripheral vascular complications, precerebral artery stenosis, previous cerebrovascular incident, bleeding disorder, or intermittent claudication and pulmonary diseases were excluded from the study. Twelve patients were given synthetic PGE_1 infusion (20 ng · kg^{-1} · min^{-1}) from the induction of anesthesia to the end of the operation in a double-blind manner. Five hundred micrograms of synthetic PGE_1 was diluted in 500 mL of saline solution (1 μg/mL). The other 12 patients received a placebo (500 mL of saline solution) and served as controls.

Surgical Procedures

Premedication consisted of morphine sulfate, 0.1 mg/kg intramuscularly, and scopolamine hydrobromide, 0.4 mg. Anesthesia was induced with sodium thiopental, 3 to 5 mg/kg, followed by pancuronium bromide, 0.1 mg/kg. Fentanyl was given in incremental doses during induction of anesthesia and after intubation. All operations were performed through a midline sternotomy using ECC with cannulation of the ascending aorta and right atrium. A Maxima membrane oxygenator (Medtronic, Inc) and general hypothermia of 28° to 31°C were used in all instances, and the myocardium was protected by modified St Tho-

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Table 1. Summary of Patient Data by Group

Variable	Alprostadil Group (n = 12)	Control Group (n = 12)
Age (y)	64.5 ± 2.07	64.42 ± 1.6
Sex	Male	Male
ECC time (min)	95 ± 6.5	104.34 ± 6.7
Aortic cross-clamp time (min)	55 ± 4.95	64.92 ± 5.27

ECC = extracorporeal circulation.

mas' cardioplegic solution (Pharmacia, Uppsala, Sweden).

Use of Artificial Respirator After ECC

The duration of artificial respirator use during the first 24 postoperative hours was recorded for each patient. The times were compared between the PGE_1 and control groups.

Gas Analysis After Extubation

Blood gas analysis was performed in each patient every 4 hours for the first 24 hours after extubation. All patients had a respiration rate lower than 18 breaths per minute and received nasal O_2 at 2 L/min during this period. A carbon dioxide tension greater than 45 mm Hg (6 kPa) was considered a hypercapnic value, and an oxygen tension lower than 79.5 mm Hg (10.6 kPa) was considered a hypoxic value. If patients experienced hypoxia during the study, the O_2 content of the inspired air was increased. Fifteen minutes before each gas analysis, the O_2 level was reduced to 2 L/min. In hypercapnic patients, O_2 was similarly increased, and the patients were given extra breathing exercises to wash out the carbon dioxide. The O_2 was reduced to 2 L/min 15 minutes before gas analysis. If the values of the oxygen tension and carbon dioxide tension remained abnormal after the study, the patient was put on a regimen of bronchodilators and given low doses of furosemide (5 to 10 mg four times a day) to reduce subsequent accumulation of interstitial fluid.

There were two indications for extubation: the patient was adequately awake to breathe in a regularly spontaneous manner with no signs of neurological deficit, and the O_2 content in the inspired air was less than 40%, giving normal blood gases and tissue O_2 saturation of 96%. After discontinuation of the respirator, the patients were allowed to breathe with the tracheal tube in place for about 30 minutes. The inspired air mixed with O_2 of 2 L/min with the result that the tissue O_2 was maintained at a level greater than 96%. The patients were then extubated, and O_2 flow in the nasal catheter was reduced gradually to 2 L/min. Before extubation was considered, the chest roentgenograms were checked to exclude severe atelectasis, pleural effusion, pulmonary edema, and spontaneous pneumothorax. Cardiac and hemodynamic functions should also be stable.

Statistical Analysis

All means were expressed with one standard error. Comparisons between groups for one set of observations were done by the appropriate *t* test, and multiple observations were analyzed by the 2-factor analysis of variance. The percentages were compared by the method described by Swinscow [7]. The mean and the standard error were obtained and the appropriate tests for significance performed using the Statview program of the Macintosh computer SE (Apple Computer Inc). A *p* value of less than 0.05 was considered significant.

Results

Time of ECC and aortic cross-clamp time are included in Table 1. All the patients were still intubated at the end of the operation. The mean postoperative respirator time for the synthetic PGE_1 group was 5.25 ± 1.81 hours versus 8.34 ± 4.35 hours for the control group ($p = 0.047$ by *t* test) (Fig 1). The proportion of patients still intubated 6 hours after the end of the operation was 16.7% (2 patients) in the PGE_1 group and 50% (6 patients) in the control group ($p < 0.05$).

Hypercapnic tendencies after extubation were generally less common in the synthetic PGE_1 group (23.6%, 17 of 72 gas analyses in 12 patients in 24 hours) than in the controls (40.3%, 29 of 72 gas analyses in 12 patients in 24 hours) (Fig 2). The proportion of patients who showed a hypercapnic tendency every 4 hours in the first 24 hours after extubation in the PGE_1 group was 33.3%, 25%, 25%, 25%, 16%, and 16%. Respective values in the control group were 50%, 42%, 42%, 42%, 33.3%, and 33.3%. Comparison of the individual values of carbon dioxide tension with respect to the frequency of hypercapnia every 4 hours between groups using analysis of variance showed a lesser frequency in the PGE_1 group ($p = 0.0001$) (Fig 3).

The oxygen tension values after extubation were reduced to hypoxic levels in 15.3% of patients in the synthetic PGE_1 group (11 of 72 gas analyses in 12 patients in 24 hours) compared with 27.8% of the controls (20 of 72 gas analyses in 12 patients in 24 hours) (see Fig 2). The

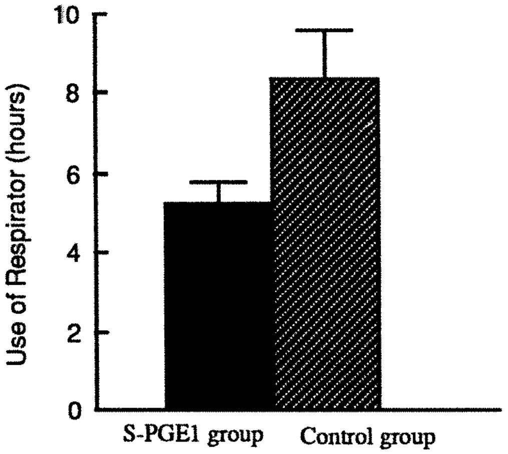

Fig 1. The mean duration of respirator use with the standard error for each group (p = 0.047, synthetic prostaglandin E_1 [S-PGE1] group versus control group).

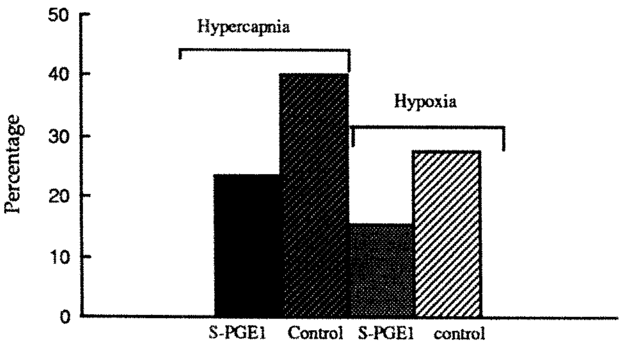

Fig 2. Percentages of patients with hypercapnia and hypoxia in the first 24 hours after extubation in synthetic prostaglandin E_1 (S-PGE1) and control groups.

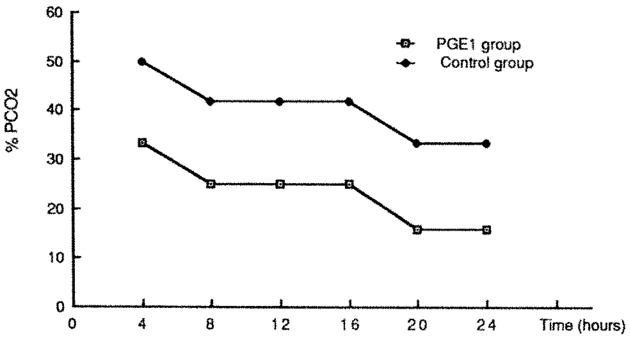

Fig 3. Percentage of patients with hypercapnic tendencies in the first 24 hours after extubation (p = 0.0001, synthetic prostaglandin E_1 [S-PGE1] group versus control group).

proportion of patients who showed a hypoxic tendency every 4 hours in the first 24 hours after extubation in the PGE_1 group was 25%, 16%, 16%, 16%, 8.4%, and 8.4%. Respective values in the control group were 42%, 33.3%, 33.3%, 25%, 25%, and 8.4%. Comparison of the individual values of oxygen tension with respect to the frequency of hypoxia every 4 hours between groups using analysis of variance showed a lesser frequency in the PGE_1 group (p = 0.0001) (Fig 4).

The mean values ± the standard errors for carbon dioxide tension and oxygen tension every 4 hours in the first 24 hours after extubation are shown in Table 2.

Comment

The lung is the organ most commonly associated with ECC–induced injury [8]. Many factors are involved in precipitating such effects. Exposure of blood to foreign surfaces and abnormal conditions initiates a systemic inflammatory response including activation of the complement system, coagulation, and complement cascades and involves both mature and premature blood elements that normally act at sites of injury [9]. The end result is leukocyte activation and subsequent deposition in the lungs and other organs [8]. Transpulmonary leukocyte sequestration occurs during partial bypass [10]. The release of oxygen free radicals and lysosomal enzymes from activated neutrophils during pulmonary reperfusion may also contribute to the causation of pulmonary dysfunction after ECC [11, 12]. Partial loss of the rheological characteristics of the blood cells leads to plugging of the microcirculation with aggregations of blood elements [13], thereby reducing pulmonary function.

Prostaglandin E_1 seems to prevent the generation of oxygen free radicals and lysosomal enzymes through special receptors on polymorphonuclear leukocytes [14–16]. It has also been shown to prevent leukocyte aggregation in the pulmonary vasculature during ECC [2]. Because PGE_1 is acknowledged to be an anti–platelet aggregation agent, these salutary effects on neutrophils are perhaps not altogether surprising.

In this study, the patients treated with synthetic PGE_1 during ECC had a shorter duration of respirator use and better postoperative blood gases. Thus, less O_2 therapy was needed for this group during the postoperative course. The stabilizing effect of synthetic PGE_1 on the lysosomes in the polymorphonuclear leukocytes prevented the release of destructive proteolytic enzymes by these cells, thereby reducing the surrounding lung tissue damage. In addition, the prevention of leukocyte aggregation in the pulmonary vasculature, the decrease in blood cell deformability, and the prevention of platelet aggregation would be expected to improve the pulmonary microcirculation and hence facilitate gas exchange in the alveoli. Another possible mechanism is that the inhibitory effect of synthetic PGE_1 on the release of oxygen free radicals might reduce the risk of damaging type 2 pneumonocytes, thereby maintaining the surfactant system during ECC, which is highly desirable to keep normal pulmonary function.

A low dose of alprostadil, 20 ng · kg^{-1} · min^{-1}, was used to avoid the possible hemodynamic side effects resulting from the vasodilating action of the drug. The patients were also selected not to be at risk in case hypotension did develop during ECC. Some authors [17, 18] have reported that the use of PGE_1 and prostaglandin I_2 (prostacylin) was associated with hypotension during ECC. However, this was not found to be associated with a significant difference in cerebral damage or neurological

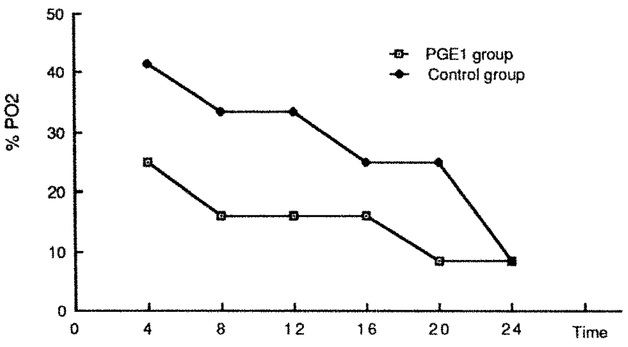

Fig 4. Percentage of patients with hypoxic tendencies in the first 24 hours after extubation (p = 0.0001, synthetic prostaglandin E_1 [S-PGE1] group versus control group).

Table 2. Values for Carbon Dioxide Tension and Oxygen Tension Measured Every 4 Hours for the First 24 Hours After Extubation[a]

	Pco_2		Po_2	
Hours	Alprostadil Group (mm Hg)	Control Group (mm Hg)	Alprostadil Group (mm Hg)	Control Group (mm Hg)
4	40.725 ± 1.35 (5.43 ± 0.18)	42.3 ± 1.58 (5.64 ± 0.21)	87.9 ± 3.75 (11.72 ± 0.5)	85.5 ± 3.75 (11.4 ± 0.5)
8	39.6 ± 1.425 (5.28 ± 0.19)	42 ± 1.5 (5.6 ± 0.2)	88.5 ± 2.48 (11.8 ± 0.33)	85.73 ± 3.75 (11.43 ± 0.5)
12	40.05 ± 1.88 (5.34 ± 0.25)	42.75 ± 1.58 (5.7 ± 0.21)	88.8 ± 3 (11.84 ± 0.4)	91.5 ± 3.3 (12.2 ± 0.44)
16	40.5 ± 1.43 (5.4 ± 0.19)	45 ± 1.35 (6 ± 0.18)	88.88 ± 3 (11.85 ± 0.4)	88.5 ± 3.08 (11.8 ± 0.41)
20	38.55 ± 1.13 (5.14 ± 0.15)	40.5 ± 1.43 (5.4 ± 0.19)	92.1 ± 2.48 (12.28 ± 0.33)	85.5 ± 3 (11.4 ± 0.4)
24	38.85 ± 1.13 (5.18 ± 0.15)	40.5 ± 1.58 (5.4 ± 0.21)	91.73 ± 2.85 (12.23 ± 0.38)	89.25 ± 2.93 (11.9 ± 0.39)

[a] Data are shown as the mean ± the standard error. [b] Numbers in parentheses are kilo Pascals.

disorders [18]. One group [19] described potential clinical advantages for the use of PGE_1 infusion in children during ECC to be adequate diuresis and preservation of platelet function and count with a mean arterial blood pressure higher than 60 mm Hg during ECC. Another group [20] reported that with infusion of PGE_1, the mean arterial blood pressure during ECC in adults was 40 mm Hg compared with 60 mm Hg in controls. Other advantages included lower systemic vascular resistance and faster recovery from hypothermia. This has led to the suggestion that the negative hemodynamic side effects of the vasodilating prostaglandins are probably counteracted by the beneficial actions of these agents [18, 20].

We think that the improvement in the blood rheology shown by some prostaglandins is of importance in this aspect, as it may contribute to the blood flow in the cerebral microcirculation and thus provide a natural counterprotective mechanism against the induced hypotension. Maintenance of the microcirculation in the different parts of the body will help it withstand the low blood pressure. In our initial use of alprostadil with doses higher than the present dose, there was a substantial risk of marked hypotension during ECC. In this study, there was a reduction in mean blood pressure during ECC of about 10 mm Hg in the treated patients compared with the controls. However, the lowest recorded blood pressure during ECC in the synthetic PGE_1 group was 30 mm Hg. After ECC, the mean blood pressure in both groups was comparable. No patient had a postoperative neurological complication.

These results suggest that the continuous infusion of a low dose of synthetic PGE_1 during a cardiac operation with ECC may reduce the damaging effects of ECC on lung tissue. Although the precise mechanism behind this is not fully understood, several pharmacological interactions seem to be involved. In addition, the potential for a reduced respirator time and better pulmonary function after ECC for cardiac surgical procedures is of great benefit not only to the patients but also to the resources of the health delivery organizations.

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REVIEW OF RECENT BOOKS

Care of the Patient With Previous Coronary Bypass Surgery
Edited by David D. Waters, MD, FRCP(C), FACC, and
Martial G. Bourassa, MD, FRCP(C)
Philadelphia, F.A. Davis, 1991
287 pp, illustrated, $75.00

Reviewed by George J. Kontos, Jr, MD

Physicians and surgeons can find comprehensive guidance on every aspect of management of patients after coronary artery operations in this book. In the excellent tradition set forth by the Cardiovascular Clinics Series, this book provides valuable information.

The authors begin by discussing, in detail, early postoperative management and cardiac rehabilitation in patients after coronary artery bypass operations. A thorough discussion of various factors influencing the long-term results of bypass grafts is particularly useful. A sequential pathologic analysis of vein grafts, internal mammary artery grafts, and native coronary vessels is presented along with beautiful illustrations. Moreover, a clinical approach to the management of cardiac symptoms in the patient after bypass is particularly noteworthy. Unlike all other chapters in this book, the chapter on the technical considerations in reoperation for coronary artery bypass grafting is much less comprehensive.

Overall, the text is well written and particularly informative. This book provides an excellent resource for all physicians and surgeons caring for patients with previous coronary artery bypass operations.

San Antonio, Texas

Breast Development and Areola Sensitivity After Submammary Skin Incision for Median Sternotomy

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Vertical incision for median sternotomy may result in unsightly scars. Therefore we have used a horizontal approach in women since the early 1980s. Of 36 women, 27 came for a follow-up examination. A tendency toward scar hypertrophy was found medially in 7 women. Four breast-fed their child after operation. Reduced areola sensitivity occurred in only 9 women. Horizontal submammary skin incision resulted in cosmetically acceptable scar formation and did not harm breast development and lactation.

(Ann Thorac Surg 1992;53:1023–4)

The median sternotomy through a vertical skin incision is the most preferred approach to the heart. The cosmetic result of the scar may be unsatisfactory. Especially in women the scar is conspicuous, and it cannot be hidden with female clothing. Therefore a horizontal incision is often recommended, but the long-term outcome of this skin incision regarding scar formation, breast development, areola sensation, and breast function has not yet been evaluated. Therefore we examined these specific questions in 27 women 8 to 10 years after an open heart operation with a submammary skin incision.

Patients and Methods

In 36 women a horizontal submammary skin incision was used 8 to 10 years ago. The reasons for the operation were congenital heart failures. The mean age of the patients was 13 years (range, 3.5 to 30 years) at the time of operation and 23.3 years (range, 13 to 38 years) at the time of follow-up. The operations were performed by different surgeons. Twenty-seven patients came to a follow-up examination. We examined the location and width of the scar, breast symmetry, areola sensitivity to light touch, and lactation after birth of a child. A questionnaire was designed to evaluate the patient's contentment.

Results

Scar Formation

In 19 patients a straight horizontal incision was used [1]; in 8 patients the incision was raised upward toward the level of the nipple medially [2]. In 15 patients the scar was placed in the submammary crease, and in 4 patients the scar was placed beneath the submammary crease. In 8 patients the scar was placed too high above the submammary crease. Six of those patients were operated on before the onset of breast development. This might have been the reason for the upward location of the scar. A tender scar with maximum width of 1 cm was seen in 25 patients in the submammary crease (Fig 1). Two patients showed hypertrophic scars laterally in the submammary crease; 7 showed hypertrophic scars medially. In 5 of them the incision was raised medially up toward the level of the nipple. In 1 patient an ugly keloid with slight distortion of the breasts developed (Fig 2). Overall, 21 patients were very pleased with the cosmetic result after horizontal submammary skin incision, 5 were less content, and 1 was not content at all. Only 1 patient felt handicapped by the scar in the selection of clothing.

Breast Symmetry

A slight breast asymmetry was noticed in 4 patients, and in 1 of them the incision was placed above the submammary crease.

Sensitivity

The areola sensitivity was unimpaired in 18 patients. Seven patients complained of decreased sensitivity in one areola. Two patients complained of bilateral diminished sensitivity. The areola sensitivity increased within 2 years after operation. Ten patients complained of diminished sensitivity in the sternal region.

Breast-Feeding

Six patients gave birth to a child postoperatively. Four of them breast-fed their child, whereas 2 gave it up after a short time due to reduced lactation.

Comment

Scar Formation

The scar is often the only reminder of a cardiac operation. Because scar formation is not predictable, care should be taken not to leave scars in exposed areas like the sternal region, where especially women are more likely to have development of unsightly scars after vertical incision for median sternotomy [3]. All kinds of incisions that cross Langer's lines of tension may result in poor scars. Using a vertical skin incision, the Langer's lines are crossed at a

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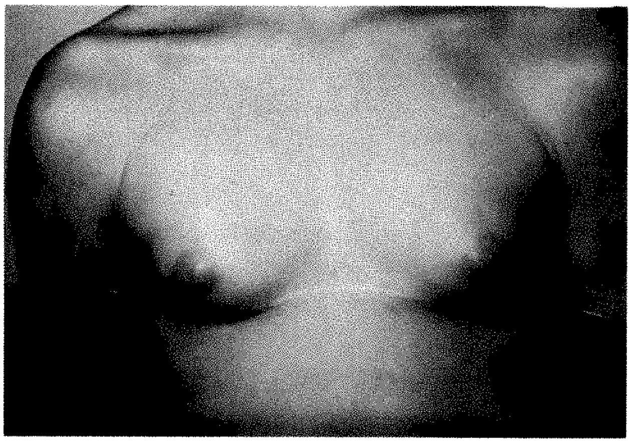

Fig 1. Inconspicuous scar after horizontal submammary skin incision.

right angle [4], whereas the submammary horizontal incision can be placed along the Langer's lines. The positive effects on the scar are reported in the literature [1, 2, 5]. In some of our patients the scar was not formed in the same way throughout the whole incision site. Medially it was prone to hypertrophy, especially when the incision was elevated up to the nipples. This was also noticed in patients after reduction mammoplasty, in whom the scar medially often appeared hypertrophied, especially in young patients [6]. Therefore it is better to use a straight horizontal incision to avoid this critical area. Nearly all of our patients were content with the scar because it could be hidden very well by any type of clothing.

Breast Symmetry

Because the submammary skin incision is frequently used in young girls for cosmetic reasons, it is interesting to investigate the influence on breast development. A slight breast asymmetry could be found in 4 patients; in 1 of them the high incision might have been the reason. In performing a submammary horizontal incision in children it is essential not to place the incision too high, because this might cause distortion of the developing breast.

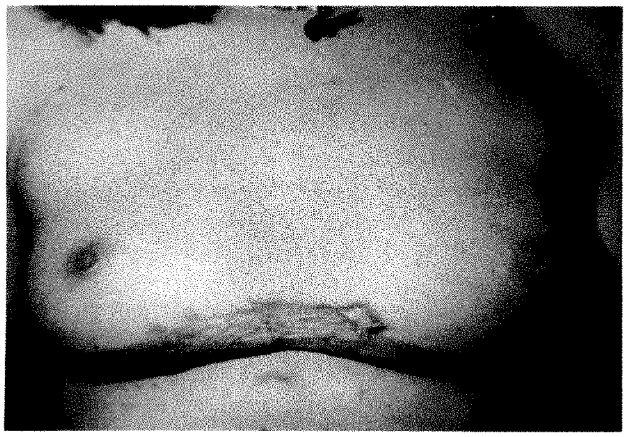

Fig 2. Keloid medially with slight distortion of the breasts after horizontal submammary skin incision.

Sensitivity and Breast-Feeding

The main nerve supply for the nipple areola complex is provided by branches of the third to sixth lateral intercostal nerves and medially by branches of the second to sixth intercostal nerves [7]. Postoperatively diminished areola sensitivity was restored in nearly all patients after 2 years. A deficiency of sensitivity in the sternal region, however, was detected in nearly one third of our patients. Areola sensitivity is important for eliciting a neurohormonal reflex action for breast-feeding [8]. During operation both breasts are mobilized from the pectoral fascia, and the median blood supply from the mammarian artery is completely interrupted. This does not seem to have an adverse effect on blood supply and subsequent breast development, as 4 of our patients had normal lactation after delivery. Basically breast-feeding is possible after a horizontal submammary skin incision for median sternotomy. It is essential to instruct the patients before operation and to encourage them during pregnancy that breast-feeding is probably possible also with scars in the breast region and no complication has to be expected.

Conclusion

From our follow-up we can conclude that the horizontal submammary skin incision results in a cosmetically acceptable scar formation. A straight horizontal incision medially should be preferred to a curved one. Breast development is not disturbed. No adverse effect on the ability to breast-feed was detected. The reduced areola sensitivity or sensitivity in the sternal region, which occurred in some patients, was not designated as serious by them.

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Skeletal Muscle Ventricles With Improved Thromboresistance: 28 Weeks in Circulation

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Skeletal muscle ventricles (SMVs) were constructed from the left latissimus dorsi in 22 mongrel dogs. The configuration of these SMVs was different from those previously reported. The animals were divided into two groups: group A (n = 11) SMVs rested for 10 weeks after construction; group B (n = 11) SMVs rested for 18 weeks. At the end of the delay period, SMVs were tested in vivo with a mock circulation device. The SMVs in group B developed stroke work greater than those in group A. After acute testing, SMVs (n = 12) were connected to the descending thoracic aorta and stimulated to contract during diastole. Aortic diastolic counterpulsation was achieved in all dogs, with 9 animals surviving from 1 to beyond 28 weeks. In all of the dogs surviving 1 week or more, the SMVs remained free of thrombus. Aspirin was used as the only antithrombotic agent. Skeletal muscle ventricles in this study were able to develop stroke work similar to that previously reported, intermediate between that of the right and left ventricular stroke work, with a significantly decreased incidence of thromboembolism.

(Ann Thorac Surg 1992;53:1025–32)

Skeletal muscle pumps have functioned as effective aortic diastolic counterpulsators [1–11]. In acute experiments skeletal muscle ventricles (SMVs), connected to either a mock circulation or in circulation, have developed stroke work intermediate between that of the native right and left cardiac ventricles [8–10, 12–14]. In our first chronic in-circulation experiment SMVs functioned effectively for several weeks, but the longest surviving dogs died of complications related to thromboembolism [1]. In a more recent study SMVs pumped blood effectively in the circulation for more than 1 year [2, 3, 11]. The incidence of thromboembolism and SMV thrombus was less than in the earlier study, but now laminar clot in the apex of the SMV has developed in even the longest surviving dog from that study [11].

The purpose of this study was to attempt to improve on our previous results by changing the geometry of the SMVs, particularly trying to minimize the thromboembolic complications. We also attempted to determine whether the length of vascular delay influenced SMV performance.

Material and Methods

Skeletal muscle ventricles were constructed from the left latissimus dorsi muscle in 22 mongrel dogs. The animals were operated on in accordance with the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences (NIH publication No. 85-23, revised 1985). Anesthesia was induced by intravenous thiamylal (15 mg/kg). The animals were then intubated and connected to a ventilator, and anesthesia was maintained by the use of isoflurane (1% to 2%). Prophylactic antibiotics were used, with intravenous cefazolin (1 g) administered upon induction and every 6 hours thereafter until the animals were fully awake. Cephalexin (60 $mg \cdot kg^{-1} \cdot day^{-1}$) was then given orally for 14 days after operation. The left latissimus dorsi muscle was dissected from the chest wall, and all distal blood vessels were ligated. The main neurovascular pedicle was left intact. A modified electrode (model 6901; Medtronic, Inc, Minneapolis, MN) was placed around the thoracodorsal nerve. The muscle was wrapped in a spiral fashion around a mandrel made of a Lycra shell, ovoid in shape (major axis, 6.3 cm; minor axis, 4.3 cm) and filled with silicon oil (Aldrich Chemical Co, Milwaukee, WI). The mandrel was manufactured according to our specifications by Medtronic, Inc.

The muscle was wrapped differently from SMVs in previous reports. The ventral portion of the left latissimus dorsi (*A* in Figure 1), which has the largest muscle length and mass, was wrapped around the apex of the mandrel, with the shorter dorsal aspect of the muscle (*B* in Figure 1) making up the base of the SMV. In our previous studies the ventral portion of the latissimus dorsi was wrapped around the base with the dorsal part making up the apical portion of the SMV [2, 8, 15]. About 1¾ to 2 wraps of muscle were obtained. A Dacron felt (Bard Cardiosurgery, Billerica, MA) collar was attached to the top of the mandrel to which the muscle wraps were sutured.

Through a small thoracotomy, two sensing electrodes

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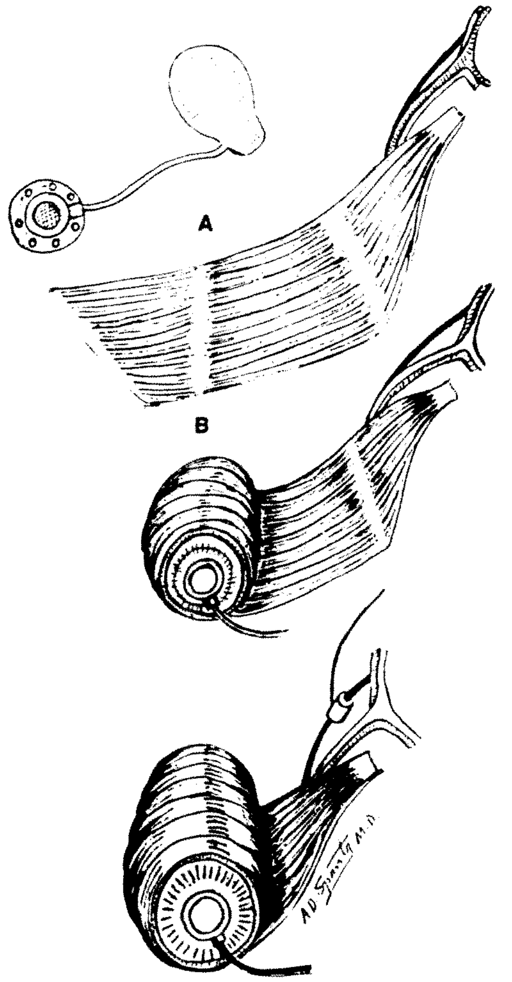

Fig 1. Construction of a skeletal muscle ventricle from the latissimus dorsi muscle. All chest wall connections are divided, whereas the neurovascular pedicle is kept intact. A nerve lead is placed around the thoracodorsal nerve. The ventral portion of the muscle (A) is wrapped around the apical portion of the mandrel. The dorsal portion of the muscle (B) is wrapped around the base of the mandrel and is sutured to a Dacron felt collar.

(model 6917; Medtronic, Inc) were placed on the left ventricular epicardium and tunneled below the left rectus muscle. All wounds were then closed in layers with the SMV left subcutaneously outside the chest. Through a left neck incision, the left carotid artery was exposed, and then a subcutaneous carotid loop was created to allow for easy percutaneous access at a later time.

The dogs were divided into two groups. In group A (n = 11), the SMVs were allowed a rest period of 10 weeks. In group B (n = 11), the SMVs received a delay of 18 weeks. In group A, wound infections developed in 2 dogs within the first 10 days after operation, and these dogs were excluded from further study. In 3 additional animals, a leak occurred in the mandrel, with subcutaneous infiltration of silicon oil. These animals were also excluded from the study (2 from group A, 1 from group B). The final composition of the two groups is shown in Table 1. At the end of vascular delay periods the animals were anesthetized, and the Lycra shell mandrels were removed from the SMVs. At that time the inner aspect of the SMV was noted to be lined by a smooth tissue layer formed by the reaction induced by the Lycra mandrel.

Table 1. Experimental Groups

Group	n	Dog Weight[a] (kg)	Mandrel Volume[a] (mL)	Delay (wk)
A	7	12.8 ± 1.0	54 ± 2.0	10
B	10	13.4 ± 0.7	54 ± 2.6	18

[a] Values are mean ± standard error of the mean.

Mock Circulation

The SMVs were connected to a mock circulation device. This device was not connected to the circulation. The mock circulation device has been described before [12–14, 16, 17], and its features are illustrated in Figure 2. The mock circulation allows for control of both preload and

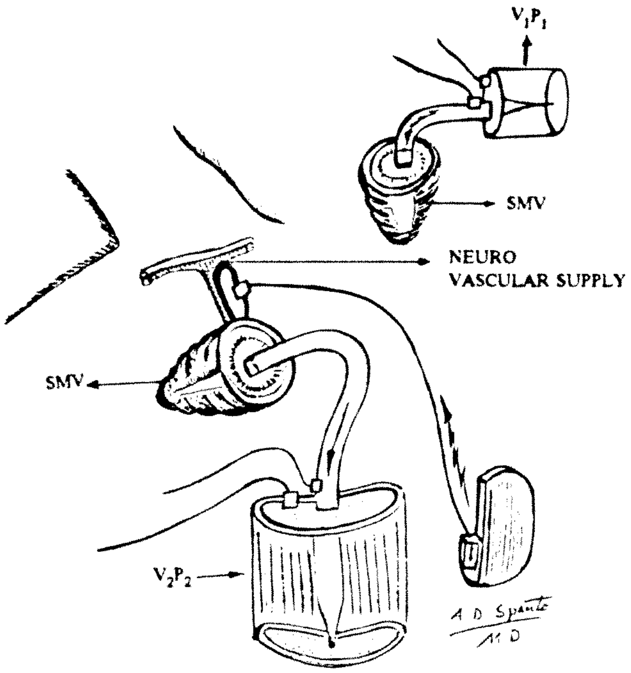

Fig 2. A skeletal muscle ventricle (SMV) is connected to the mock circulation device. A rigid Plexiglas tube connects a latex bladder. That bladder is placed inside the SMV cavity. The other end of the Plexiglas tube is connected to a polyurethane bladder inside a pressurized canister. Skeletal muscle ventricle end-diastole and end-systole are shown in the diagram. The pressure in the canister is the afterload. The pressure in the saline chamber is the preload. Upon implantation of the device during the operation, the bladders and conduit were completely filled with saline solution. The canister is pressurized with air. The fluid-filled conduit is vented so that the canister bladder collapses completely. A valve is effectively produced by the collapsed bladder within the canister, thus isolating the pressure in the canister (P_1) from the pressure in the SMV when the SMV is at rest. This permits independent adjustment of filling pressures (preload) within the SMV and independent adjustment of the canister air pressure (afterload). Given the closed system, Boyle's law applies: $V_1P_1 = V_2P_2$.

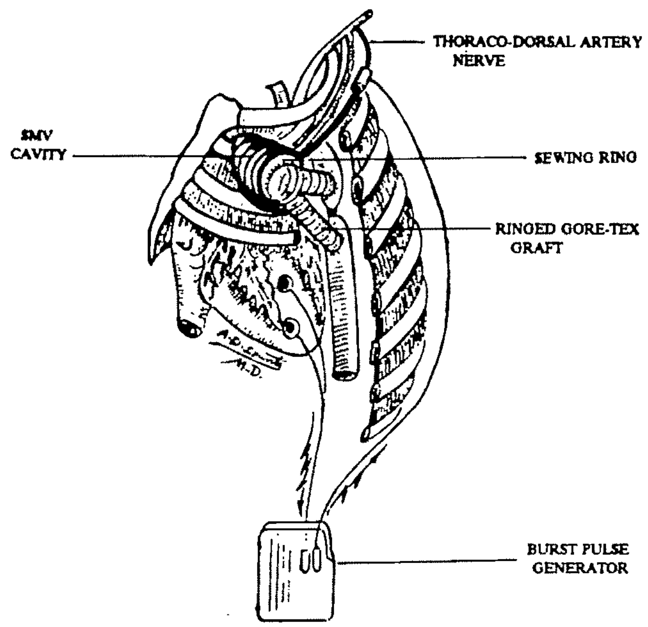

Fig 3. Diagram of skeletal muscle ventricle (SMV) *outside the chest, with the apex along the anterior axillary line and the base along the posterior axillary line. Two conduits connect the SMV to the aorta. The aorta is ligated between the limbs of the conduits to allow all aortic flow to pass through the SMV. Two epicardial leads are used for sensing, and one bipolar nerve lead is used to stimulate the thoracodorsal nerve.*

afterload. An analytical solution for the calculation of stroke work (SW) using this device has been derived [14]:

$$SW = P_1V_1 [\ln(V_1) - \ln((P_1/P_2)V_1)] - P_3V_1 [(1 - (P_1/P_2)],$$

where P_1 = afterload, P_2 = SMV systolic pressure, P_3 = preload, and V_1 = canister volume.

For testing with the mock circulation, the nerve electrodes were connected to a burst generator (model 7421; Medtronic, Inc) set at the following parameters: duty cycle = 310 milliseconds on, 1.5 seconds off; amplitude = 4 V (supramaximal); pulse width = 210 milliseconds. These settings were identical to those used in previous mock circulation studies from this laboratory [17] and were chosen to allow for some comparison with previous work. For both groups, measurements were obtained in an identical fashion, first at an afterload of 30 mm Hg and then at an afterload of 80 mm Hg. At the afterload of 30 mm Hg the preload was increased gradually from 0 to 25 mm Hg. At the afterload of 80 mm Hg the preload was increased slowly from 0 to 60 mm Hg. Recordings were obtained first at a stimulation frequency of 25 Hz and then repeated at a stimulation frequency of 85 Hz.

In Circulation

After the acute testing SMVs were connected to the circulation in 13 dogs, as depicted in Figure 3. In 2 of the original 22 dogs it was decided not to place the SMVs in circulation because the base of the SMV (where ruptures had occurred in the past) was particularly thin [2]. In a further 2 dogs, SMVs were connected from the left ventricle to the aorta as left ventricular assist devices; this connection was abandoned early on in this study because of poor results. Immediately after connection, an ischemic injury developed in one of the SMVs, most likely due to torsion of the neurovascular pedicle, and this SMV was excluded from further analysis.

The descending thoracic aorta was exposed through a left thoracotomy, with partial removal of the third rib. Two reinforced polytetrafluoroethylene vascular grafts (Gore-Tex; W.L. Gore & Associates, Inc, Flagstaff, AZ) 14 mm in diameter were then anastomosed to the aorta, one immediately distal to the left subclavian artery and the other approximately 5 cm distal to the left subclavian artery. The other ends of the vascular grafts were sewn together to form a bifurcation, and then the resulting single lumen was sewn to the Dacron collar of the SMV (see Fig 3). When all anastomoses were completed, and after the system had been deaired, the vascular clamps were released. The aorta was immediately ligated between the limbs of the two grafts so that there was obligatory blood flow through the SMV (see Fig 3).

The sensing leads and the nerve electrode were connected to an implantable R-wave synchronous stimulator (Prometheus; Medtronic, Inc), which was programmed to stimulate the motor nerve to the SMVs during diastole at a 1:2 ratio with the cardiac cycle up to a heart rate of 120 beats/min and at 1:3 at a heart rate above 120 beats/min. The pulse amplitude used was 2.5 V. A stimulation frequency of 33 Hz was used chronically. A frequency of 50 Hz was used temporarily during pressure measurements starting at 1 week postoperatively. A stimulation frequency of 33 Hz was used because it yields a more forceful muscle contraction than 25 Hz and seems well tolerated chronically by the muscle from most reports dealing with cardiomyoplasty. The chest wound was closed in layers over a drain, and the pacemaker was secured below the left rectus abdominis muscle. All drains were removed after 12 to 24 hours.

The animals were given aspirin (81 mg/day) as the only antithrombotic agent. Animals received the identical antibiotic prophylaxis to that described for the first operation. Starting at 1 week, and at regular intervals thereafter, the surviving animals were lightly anesthetized and pressure recordings were obtained from the femoral and carotid arteries through percutaneous cannulation. Two-dimensional echograms of the SMVs were also obtained at the time of pressure measurement to check for the presence of thrombus in the SMVs.

Diastolic tension time index was calculated for the longest surviving dog (dog 1) by the integration of the area under the diastolic portion of the carotid arterial pressure trace and then comparing the augmented diastole with nonaugmented diastole averaged over ten cardiac cycles.

An autopsy was performed whenever a death occurred. Biopsy samples were removed from the basal, middle, and apical portions of each SMV, and the tissue was fixed in formalin and embedded in paraffin. Sections were cut at 5-μm thickness and stained with hematoxylin and eosin for light microscopic examination.

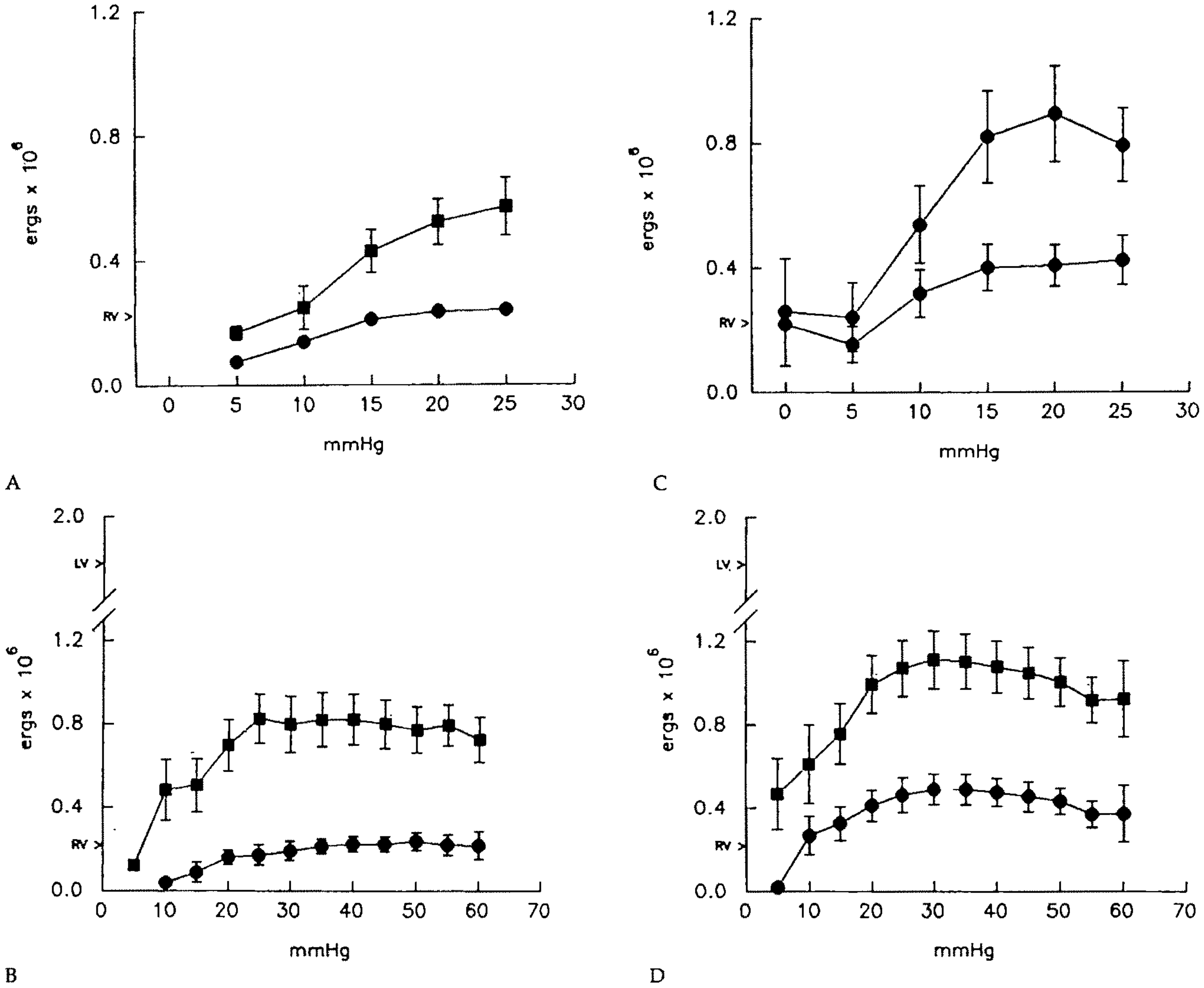

Fig 4. Stroke work is plotted versus preload for both groups. Left ventricular (LV) and right ventricular (RV) stroke work previously calculated for similar size dogs are shown for comparison (RV stroke work = 2.2 ± 1.1 × 10^5 ergs, LV stroke work = 18.3 ± 9.8 × 10^5) [10]. (A) Stimulation frequency = 25 Hz; afterload = 30 mm Hg. (B) Stimulation frequency = 25 Hz; afterload = 80 mm Hg. (C) Stimulation frequency = 85 Hz; afterload = 30 mm Hg. (D) Stimulation frequency = 85 Hz; afterload = 80 mm Hg.

Statistical significance of the observed changes was determined using an unpaired Student's *t* test. Comparison of animals in this study with those in a previous study [2] with regard to thrombus formation was done using a χ^2 test.

Results

Mock Circulation

The performance of the SMVs from the two groups when pumping against the mock circulation device at a stimulation frequency of 25 Hz is shown in Figures 4A and 4B. Canine right ventricular and left ventricular stroke work measured in similar size dogs from a previous study [10] are also shown for comparison. At an afterload of 30 mm Hg and preloads greater than 10 mm Hg, SMVs from group B developed stroke work more than 140% that of the right ventricle, whereas SMVs from group A needed a preload of 15 mm Hg to equal the right ventricular stroke work. At an afterload of 80 mm Hg and a preload greater than 5 mm Hg, SMVs from group B developed stroke output much greater than that of the right ventricle, reaching a maximum at 20 mm Hg of preload with 370% of right ventricular stroke work and 45% of left ventricular stroke work. At an afterload of 80 mm Hg, SMVs from group B performed better than those from group A. Comparison by an unpaired *t* test revealed a statistically significant difference between the two groups at more than 10 mm Hg of preload (for afterload = 30 mm Hg: $p < 0.007$ at preload = 15 mm Hg, $p < 0.002$ at preloads of 20 and 25 mm Hg; for afterload = 80 mm Hg: $p < 0.04$ at preload = 15 mm Hg, $p < 0.005$ at preloads = 20 to 60 mm Hg).

The stroke work developed by both groups against a mock circulation device at a stimulation frequency of 85 Hz is shown in Figures 4C and 4D. At both an afterload

Table 2. Outcome of Long-Term Pumping in Circulation

Dog	Delay (wk)	Length of Survival (wk)	Presence of Thrombus in SMV	Cause of Death
1	18	28	–	Alive and well
2	18	16	–	Euthanized
3	10	13	–	Rupture
4	10	10	–	Alive and well
5	18	8	–	Abscess
6	18	5	–	Rupture
7	10	2	–	Rupture
8	10	1	–	Unknown
9	10	1	–	Euthanized
10	18	<1	+	Thromboembolism
11	18	<1	+	Bleeding
12	10	<1	+	Thromboembolism

SMV = skeletal muscle ventricle.

of 30 and 80 mm Hg, higher stroke work was obtained with the more intense 85-Hz stimulation pattern. A maximum was obtained at an afterload of 80 mm Hg and a preload of 25 mm Hg, with SMVs from group B developing 477% of right ventricular stroke work and 58% of left ventricular stroke work. Comparison of the two groups by an unpaired t test showed that SMVs in group B performed significantly better than the SMVs in group A at preloads greater than 10 mm Hg (afterload = 30 mm Hg: $p < 0.04$ at preload = 10 mm Hg, $p < 0.02$ at preload of 20 and 25 mm Hg; afterload = 80 mm Hg: $p < 0.03$ at preload = 15 mm Hg, $p < 0.004$ at preload = 20 to 60 mm Hg).

In Circulation

The outcome of the animals with SMVs pumping chronically in the circulation is shown in Table 2. Dogs tolerated the SMV aortic counterpulsation well and were able to move about freely. They were tether-free in that no tubes or wires crossed the skin barrier. They had no apparent physical impairment or discomfort. Two dogs continue to do well at the time of this writing, at 10 and 28 weeks, respectively.

Significant aortic diastolic augmentation developed in all 12 dogs at both 33 and 50 Hz. Percentage of diastolic augmentation was calculated at the level of the carotid artery by comparing the peak of the augmented diastolic pressure with the diastolic pressure peak after the dicrotic notch. Percent pressure augmentation of all dogs is summarized in Table 3. At the time of connection to the circulation, SMVs from group B developed higher diastolic augmentation than those from group A. However, by week 1, no significant difference was detected in diastolic augmentation between groups A and B. The stimulation frequency of 33 Hz was used at operation and chronically thereafter. Typical pressure tracings at the chronic stimulation frequency of 33 Hz are shown for the longest surviving animal on the day of operation, at 10 weeks, and at 28 weeks in Figures 5A, 5B, and 5C, respectively. Diastolic tension time index at those times showed an improvement in the augmented diastole when compared with the unaugmented diastole of 32.4% on the day of operation, 18.8% at 10 weeks, and 20.2% at 28 weeks in that dog. Figure 6 shows the percent diastolic augmentation from the same dog at the level of the carotid artery over the period of 28 weeks. There was an initial deterioration during the first 2 weeks, but after that, the SMV in this long-term survivor resumed a function similar to that first measured at the time of operation.

Thromboembolic complications were not detected in animals that survived 1 or more weeks. Also, thrombus was not noted by echography in the SMVs of those dogs while they were alive, or at autopsy. The serum blood urea nitrogen and creatinine levels remain normal in the 2 surviving dogs (dogs 1 and 4). The 3 animals that died

Table 3. Carotid Diastolic Pressure Augmentation

	Mean Percent Carotid Diastolic Pressure Augmentation* (range)					
	Percent at 33 Hz			Percent at 50 Hz		
Time (wk)	Group A	Group B	A + B	Group A	Group B	A + B
0 (n = 12)	15 ± 1.2 (10–17)	31 ± 5.0 (14–46)	24 ± 3.7 (10–46)			
1 (n = 9)	24 (11–38)	19 (12–28)	22 (11–38)	31 (15–44)	27 (17–32)	29 (15–44)
2 (n = 7)	23 (17–29)	12 (9–16)	16 (9–29)	25 (20–30)	15 (13–18)	19 (13–30)
5 (n = 6)	15 (14–15)	20 (12–32)	18 (12–32)	18 (16–20)	27 (19–39)	23 (16–39)
8 (n = 4)	17	24 (11–33)	22 (11–33)	23	35 (18–48)	32 (18–48)
10 (n = 3)	18	18 (9–26)	18 (9–26)	25	23 (17–29)	24 (17–29)
13 (n = 2)		24 (15–33)	24 (15–33)		32 (20–43)	32 (20–43)
16 (n = 2)		22 (13–30)	22 (13–30)		26 (15–36)	26 (15–36)
18 (n = 1)		43	43		62	62
24 (n = 1)		42	42		56	56
28 (n = 1)		39	39		47	47

* ± standard error of the mean calculated only at operation (time = 0).

during the first week had clot in the SMV, and 2 of these dogs had evidence of embolism with areas of infarct detected at autopsy in the kidneys, spinal cord, and distal limbs. None of the animals, however, that survived beyond 1 week had evidence of thrombus in the SMV or distal embolization. When comparing the incidence of thrombus formation in this current study with that of another recent study where the SMVs had been constructed differently [2], the incidence of thrombus formation in the present model was significantly less ($p < 0.05$).

Skeletal Muscle Ventricle Histology

Grossly, all SMVs retained their ovoid shape when examined at autopsy. Histologic examination showed the SMV linings to be composed of a compact fibrocellular layer, with histiocytes as the main cellular component. Variable amounts of chronic inflammation were noted among the muscle fibers, with occasional areas of necrosis and both fatty and fibrotic replacement. Such changes were most evident in samples obtained from the base of the SMVs where rupture occurred. No specific feature could differentiate muscle samples obtained from group A compared with group B. Foreign-body giant cells were found in relation to suture material. Samples from the apex appeared comparatively healthier. Degenerative changes appeared most marked in those SMVs that had the worst performance. Well-organized thrombus was noted in the apex of SMVs of dogs 10, 11, and 12. Motor nerves from SMVs appeared normal microscopically.

Comment

This study indicates that the changes introduced in mandrel geometry and muscle wrapping have led to SMVs that are more thromboresistant than earlier SMVs when pumping blood in the circulation [1, 2]. This study also indicates that an increased vascular delay yields superior short-term SMV performance.

In a previous study, we had shown that SMVs with a larger cavity volume and vascular delay of 18 weeks

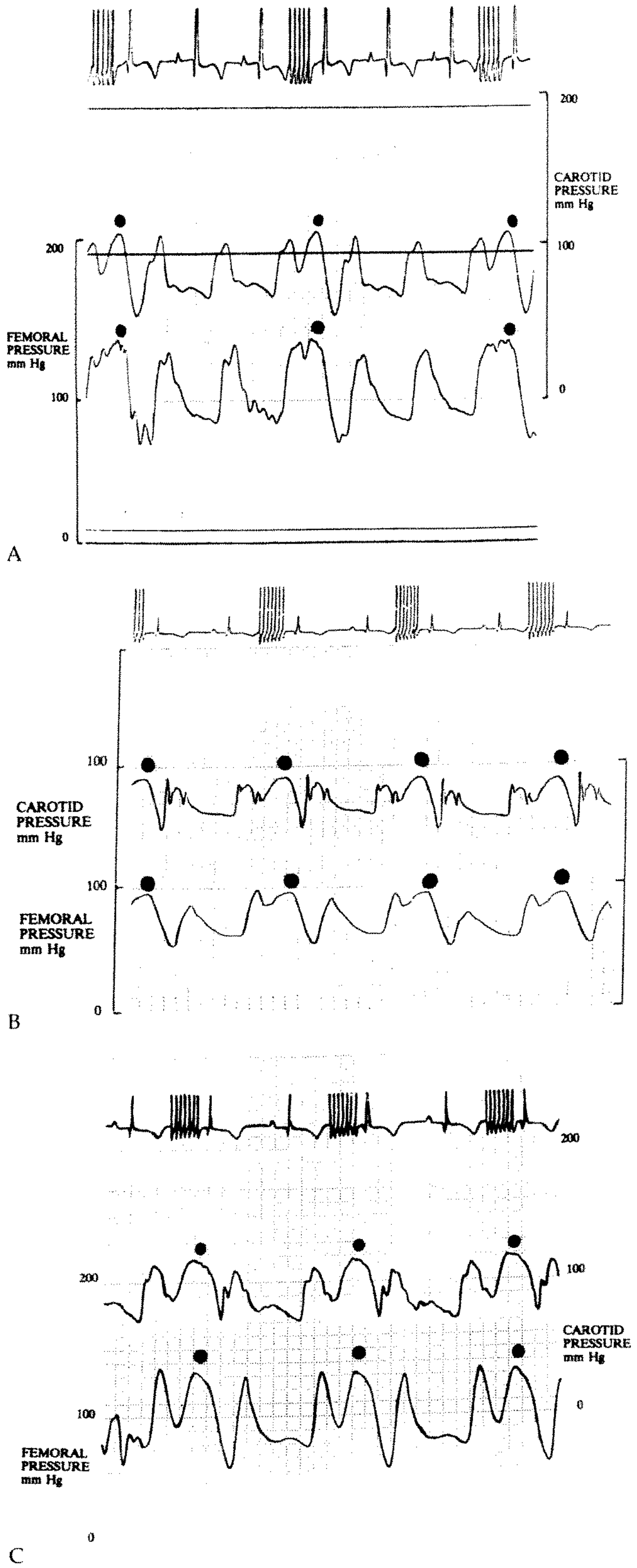

Fig 5. Pressure recordings obtained at 33-Hz stimulation in the longest surviving animal. The diastolic augmentation is marked by the black circle. *The recordings were obtained at the initial operation (A), after 10 weeks (B), and after 28 weeks (C) of continuous pumping in the circulation.*

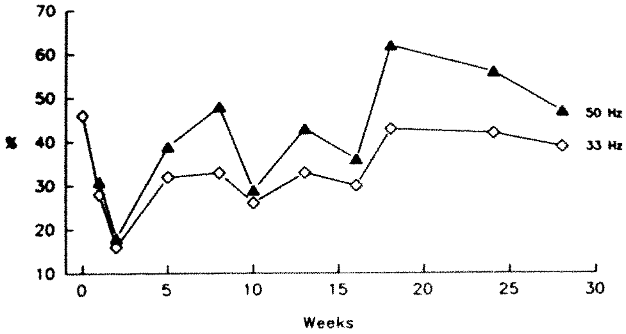

Fig 6. The percent diastolic augmentation for the carotid pressure is displayed over time for the longest surviving animal. After an early decrease, the percent augmentation returns to levels observed at operation.

developed stroke work approaching that of the canine left ventricle at physiologic preload [17]. In that earlier study, the group that received the 18 weeks of vascular delay was compared with two other groups with only 4 weeks of vascular delay. Clear superiority in work output was demonstrated with the longer rest period. In the present study, we attempted to determine whether a difference in stroke work could be detected between a 10-week and an 18-week vascular delay. Although the difference is not as striking as that in the earlier study, in this experiment the SMVs rested for longer periods also had superior performance when acutely tested in a mock circulation device.

In that previous mock circulation study, the group of SMVs with 18-week vascular delay developed greater stroke work than the group with the 18-week vascular delay in this present study. This is probably because in the present study, smaller SMV cavity volumes were used to achieve better ejection fractions at the high preloads to which SMVs would be subjected when working as aortic diastolic counterpulsators. When these SMVs were then connected to the circulation, those that had received a longer vascular delay also performed better in the circulation at the time of operation.

An important question is how the improvement in SMV function was achieved in the group with the 18-week vascular delay when compared with those with the 10-week delay. It is our experience that at the time of SMV construction, the distal one-third to one-half of the canine latissimus dorsi is severely ischemic [18, 19]. The muscle may take longer than we had previously suspected to recover sufficient vascular supply to function effectively. It is also possible that during the 18-week delay some adjustment occurred in the internal architecture and length of the muscle fibers, resulting in a more effective adaptation to the new geometry. Even though a longer vascular delay resulted in improved performance acutely, by 1 week of continuous pumping in the circulation, no difference in diastolic augmentation was detected between the two groups. Therefore, in the chronic setting the additional 8 weeks of delay appeared to offer no advantage.

In the present study, we attempted to design a mandrel around which an SMV could be constructed with reduced thrombotic complications. An ovoid mandrel was chosen in the hope of maximizing washout of blood in the apical portion of the SMV with each contraction as opposed to the conical SMV with the pointed apex that was used in our most recent previous study [2]. In our original chronic in-circulation studies, polytetrafluoroethylene-lined SMVs were used [1]. Those studies were complicated by thrombosis. This may have been a result of the surgical configuration. Tube-shaped SMVs were connected to the circulation by interruption of the aorta, which was rerouted through the SMV. In that study, good diastolic augmentation was produced, but the dogs that survived the operation died of renal failure after 5 and 11 weeks because of repeated thromboembolism from the SMV. The skeletal muscle tube ventricle was made with a larger diameter than the aorta, and this may have allowed thrombus to form at the points of anastomosis, as observed at autopsy. The configuration in the present experiment with a polytetrafluoroethylene bifurcation graft directs blood toward the round apex of the SMV. The intention was to provide effective washing in that region and, hence, reduce stasis and thrombus formation.

Prosthetic material was avoided in the SMV cavity, because this may offer resistance to SMV contraction, thus reducing the efficiency of the system. It would also prevent any prospect of growth if such an SMV were used to treat congenital heart disease. Also, because most of the prosthetic materials available are nonelastic, they would crimp when compressed, which may promote clot formation. Finally, tissue reaction to the implanted material would induce progressive fibrosis around the prosthesis, which would increase resistance to contraction and decrease filling compliance. Significant deterioration in SMV function occurred in the previous study in which a prosthetic lining was used [1].

An autogenously derived biologic lining would repair and regenerate itself. We used pleura and pericardium in a recent study [2]. The latter is used to repair intracardiac defects. Neither tissue, however, is known to have inherent thromboresistant properties. A third group of SMVs in that previous study were lined with the fibrous induced reaction from the mandrel similar to those in the present study. We did not detect a significant difference in thromboembolism when SMVs were lined with either pleura, pericardium, or the fibrotic reaction produced by the mandrel. There is evidence, however, that even the fibrous lining may be more thromboresistant than presently available prosthetic materials [20, 21].

The most important factor in reducing the incidence of thromboembolism in the present study may have been related to the change in the muscle wrapping technique. In previous chronic in-circulation animals, we had often observed by two-dimensional echography that the middle portion of the SMV displayed the best contractility. This could lead to stagnation of blood and thrombus formation in the less contractile apical portion. We also observed that those SMVs that seemed to contract more poorly were the ones that were the most prone to develop laminar clot in the apex of the SMV. By wrapping the ventral portion of the latissimus dorsi around the distal portion of the SMV we placed a larger muscle mass in the apical area. In this fashion, we hoped that blood would be cleared better from the apex with each muscle contraction. The role of aspirin to prevent thrombosis in this setting is not well defined.

With the change in the SMV construction wrap, the percent augmentation in our longest surviving dog is superior to that reported in our previous long-term studies, particularly when one compares the percent carotid diastolic augmentation from 16 to 28 weeks with that reported previously [2]. Because the chronic testing stimulation frequencies in the two studies were different (33 and 50 Hz here versus 25, 43, and 85 Hz in the previous experiment) and because there are only a few long-term survivors in each group, comparison is difficult. However it is possible that better performance could also contribute to the decrease in thromboembolic complications.

This study again demonstrates that a longer vascular delay period results in improved SMV function. However, in this study when chronic functional results were compared, no difference was detected between the group with the 10-week delay and the group with the 18-week delay. More important, however, is the decreased incidence of thromboembolic complications in chronic in-circulation animals when compared with those from previous studies. The most likely reasons for the decreased incidence of thromboembolism are related to the difference in the shape of the SMV and difference in wrapping technique. Although problems persist, this new information suggests that SMVs may become a viable alternative for the clinical treatment of heart failure.

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Contraction and Relaxation of Human Internal Mammary Artery After Intraluminal Administration of Papaverine

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The internal mammary artery has become the conduit of choice for coronary artery bypass grafting. Intraluminal papaverine treatment during operation reduces vasospasm and facilitates anastomosis. However, it has been suggested that papaverine may cause intimal damage, and accordingly we have investigated endothelial damage by comparing the responsiveness of internal mammary arteries before and after intraluminal exposure to papaverine (15 mg/mL). Control and papaverine-treated segments of internal mammary artery were obtained from 13 patients undergoing coronary artery bypass grafting and mounted as ring preparations in an organ bath. Cumulative dose contractions to noradrenaline were performed, and the dose producing a half maximal response was determined. Relaxation studies of submaximally contracted arteries were performed using the endothelium-dependent vasodilators acetylcholine and bradykinin and the endothelium-independent vasodilator sodium nitroprusside. In the human internal mammary artery the use of intraluminal papaverine increased the lumen size by 20% ($p < 0.05$), and the contractions elicited by noradrenaline were significantly less in the papaverine group than in the control group ($p < 0.05$). Endothelium-dependent relaxation to acetylcholine or bradykinin was not affected by papaverine treatment. Endothelium-independent relaxation was the same in both groups, with almost 100% relaxation achieved by sodium nitroprusside. These results indicate that intraluminal papaverine treatment during coronary artery bypass grafting causes a reduction of smooth muscle contraction and does not impair endothelium-dependent relaxation.

(Ann Thorac Surg 1992;53:1033–7)

The internal mammary artery has become the conduit of choice for coronary artery bypass grafting [1, 2] because of its superior long-term patency due to the lack of atherosclerotic changes. However, the internal mammary artery is susceptible to vasospasm during and after mobilization, which is a common arterial response to low blood flow and surgical handling [3]. To counteract this problem many centers advocate the use of papaverine during the surgical preparation of the graft. Studies have shown that papaverine prevents vasospasm and can increase the blood flow through the internal mammary artery by up to ten times [4]. Papaverine acts by inhibiting phosphodiesterase and causes an increase in cyclic guanosine monophosphate, a second messenger that induces relaxation in the smooth muscle of the vessel [5]. Papaverine can be applied either intraluminally or extraluminally depending on the preferred choice. Recent evidence, based on tissue culture studies, has suggested that intraluminal papaverine may damage the endothelium, which in turn could affect the long-term patency of the internal mammary artery [6].

After the discovery of endothelium-derived relaxing factor, considerable evidence has accumulated to show that the endothelium of many human vessels, including the internal mammary artery, plays an important role in regulating blood flow and the vascular responses of most, if not all, vascular beds. Vessels in which the endothelial lining is either damaged or removed do not show these endothelium-dependent responses [7, 8]. Accordingly we have investigated the effect of papaverine treatment on the contractile function of the internal mammary artery prepared for coronary artery bypass grafting.

Patients and Methods

This study was approved by the Leicestershire Health Authority local ethical committee in October 1990. Samples of internal mammary artery were obtained from 13 patients (10 men and 3 women), aged 46 to 63 years (mean, 56 ± 2 years), while undergoing coronary artery bypass grafting. None of the patients were diabetic but 2 were receiving treatment for hypertension.

Two samples were obtained from 11 of the patients and one sample each from the remaining 2. The first sample was obtained immediately after mobilization from the thoracic wall by diathermy and the second after intraluminal treatment with 2 mL of papaverine hydrochloride

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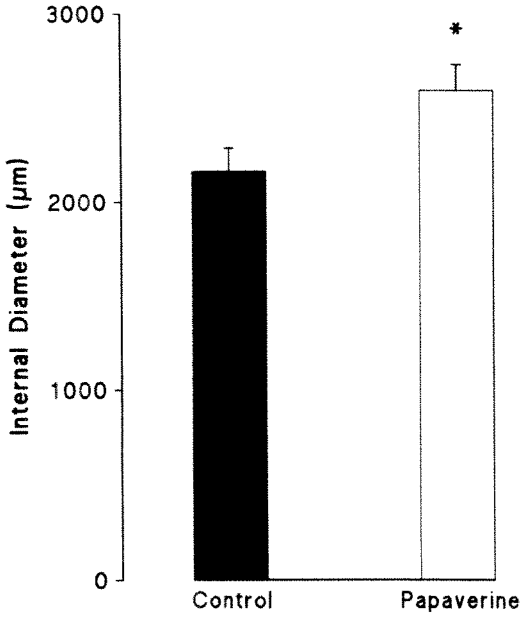

*Fig 1. Internal diameter of the control compared with the papavarine-treated internal mammary arteries (*p < 0.05).*

(15 mg/mL) for less than 5 minutes. A uniform technique of surgical dissection was used throughout. The papaverine was manually administered into the free end of the graft using an olive-tipped needle. The arterial samples were immediately placed in separate containers of cold (4°C) calcium-free physiological salt solution and stored on ice during transport from the operating theater to the laboratory.

Each segment of vessel was cleaned of connective tissue under a dissecting microscope and cut into 3-mm rings using a fixed double-bladed scalpel. The distance between the scalpel blades was measured on each occasion using Vernier calipers. The vessel rings were mounted on two stainless steel hooks (diameter, 450 µm). One hook was suspended from a force transducer (Grass FT03) and the other fixed to a plastic support arm, which was connected to a micrometer. Isometric tension was recorded using a Grass polygraph with the system being calibrated each day. The apparatus was placed in a 50-mL jacketed organ bath containing physiological salt solution (composition in millimoles per liter: NaCl, 118; KCl, 4.5; $CaCl_2$, 2.5; $MgSO_4 \cdot 7H_2O$, 1; KH_2PO_4, 1; $NaHCO_3$, 25; and glucose, 6) maintained at 37°C and gassed with 95% O_2/5% CO_2 to achieve a pH of 7.4 [9, 10]. Two organ baths were used concurrently, so that a control and treated vessel were studied at the same time. The length tension characteristics for each vessel were determined using the micrometer to move the parallel wires apart, noting the distance moved and observing the change in tension. The internal circumference, $ic = 2l + d(\pi + 2)$, was calculated where l was the distance between the wires and d was the diameter of the wires. The internal diameter was calculated from ic/π and set to $0.9 \times L_{100}$, where L_{100} is the calculated internal diameter the vessel would have had in vivo when relaxed and under a transmural pressure of 100 mm Hg [10].

After the normalization procedure was completed the rings of internal mammary artery were allowed to equilibrate for 60 minutes before a cumulative noradrenaline dose contraction curve (10^{-8} to 10^{-5} mol/L) was carried out in the presence of cocaine (10^{-6} mol/L). After further rinsing and a 20-minute interval, the vessels were submaximally contracted with noradrenaline. Upon reaching a plateau the vessels were exposed to cumulative doses of acetylcholine (10^{-8} to 10^{-5} mol/L) and the relaxation response was observed. After a further 20-minute period this procedure was repeated using bradykinin (10^{-9} to 10^{-6} mol/L) and then again with sodium nitroprusside (10^{-9} to 10^{-5} mol/L).

Tension was expressed as milliNewtons per millimeter vessel length and relaxation responses as the percent reduction in the noradrenaline-induced contraction. Results are reported as mean values (± the standard error of the mean). Significant differences were determined using analysis of variance, accepting p values less than 0.05 as being significant.

Results

The internal diameters of the two groups, at the equivalent transmural pressure of $0.9 \times L_{100}$, were significantly different. The internal diameter of the papaverine group (2,597 ± 138 µm) was approximately 20% greater than that of the control group (2,168 ± 124 µm) ($p < 0.05$) (Fig 1).

Papaverine treatment resulted in a significant reduction in the maximum contractile response to noradrenaline (control, 2.44 ± 0.39 mN/mm; papaverine, 1.43 ± 0.35 mN/mm) ($p < 0.05$) (Fig 2), and there was an increase in sensitivity shown by the dose producing 50% of the maximum contraction (control, 0.74 ± 0.15 µmol/L; papaverine, 0.32 ± 0.12 µmol/L) ($p < 0.05$). However, three of the papaverine-treated vessels failed to contract to noradrenaline, and therefore relaxation curves could not be performed on these vessels. For the purpose of analy-

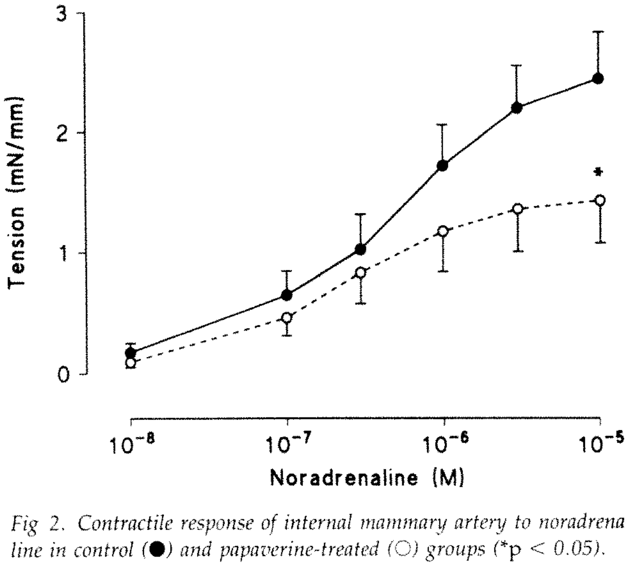

*Fig 2. Contractile response of internal mammary artery to noradrenaline in control (●) and papaverine-treated (○) groups (*p < 0.05).*

sis, the relaxation data from the three corresponding control vessels were also excluded.

Acetylcholine and bradykinin caused similar dose-dependent relaxation in both groups. Acetylcholine caused a maximal relaxation of 69% ± 12% in the control group and 67% ± 11% in the papaverine-treated group (Fig 3), whereas bradykinin induced 38% ± 17% relaxation in the control group and 50% ± 15% in the papaverine group (Fig 4). In both groups sodium nitroprusside caused complete relaxation (control, 99% ± 1%; papaverine, 98% ± 2%) (Fig 5).

Comment

The risk of internal mammary artery endothelial damage is of particular concern because of its role in regulating smooth muscle contraction by the release of endothelium-derived relaxing factor [11]. Endothelium-derived relaxing factor is released from the endothelial cells of vascular tissue in response to a variety of stimuli including an increase in blood flow, platelet-activating substances involved in hemostasis, and vasoconstrictor and vasodilator drugs [12, 13]. Vasoactive agents such as acetylcholine and bradykinin have been shown to elicit smooth muscle relaxation only in the presence of an intact endothelium [11, 14], whereas other vasodilators, such as sodium nitroprusside, are not endothelium-dependent and cause relaxation by acting directly on the smooth muscle cells increasing cyclic guanosine monophosphate concentration [15]. Therefore, endothelium-derived relaxing factor fulfills a protective role by preventing vasospasm and clot formation [16].

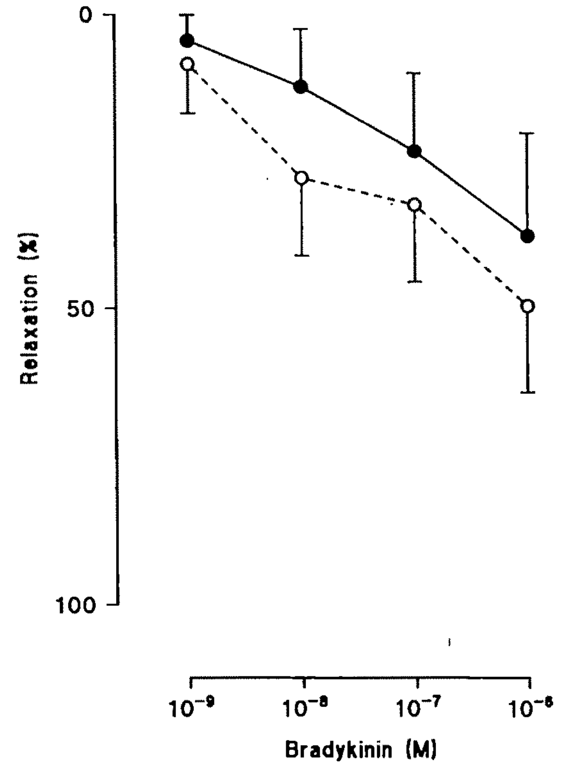

Fig 4. Relaxation response of internal mammary artery to bradykinin in control (●) and papaverine-treated (○) groups.

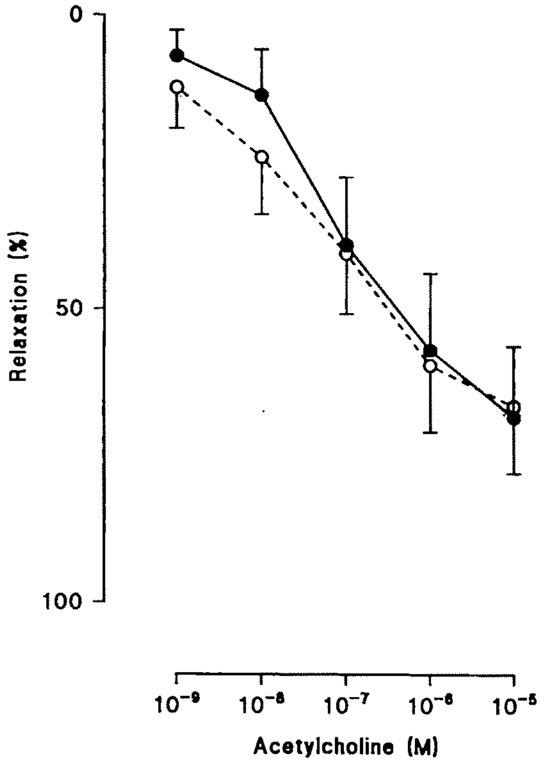

Fig 3. Relaxation response of internal mammary artery to acetylcholine in control (●) and papaverine-treated (○) groups.

The results of this study show that there is no reduction in the endothelial-dependent response to acetylcholine and bradykinin after intraluminal papaverine exposure. Maximal relaxations of 70%, induced by acetylcholine, correspond to the findings of Schoeffter and associates [7] but are lower than those found by Luscher and coworkers [16]. In this study papaverine treatment did not impair the relaxation of precontracted internal mammary arteries in response to acetylcholine. The response to bradykinin was unaltered in the papaverine group, but in keeping with other studies [7] the relaxation response to bradykinin was less than that to acetylcholine. This study failed to demonstrate functional evidence of endothelial damage; moreover, the close agreement between the responses observed in this study and previous studies suggests that the relaxation properties of these vessels were not impaired by papaverine treatment. Sodium nitroprusside is a vasodilator that acts directly on the smooth muscle using the same final pathway as endothelium-derived relaxing factor but does not require an intact endothelium for its action [15]. Sodium nitroprusside produced expected relaxations of 100% in both groups of vessels, showing that the ability of the smooth muscle to produce full relaxation was unchanged.

The significant increase in lumen diameter produced by

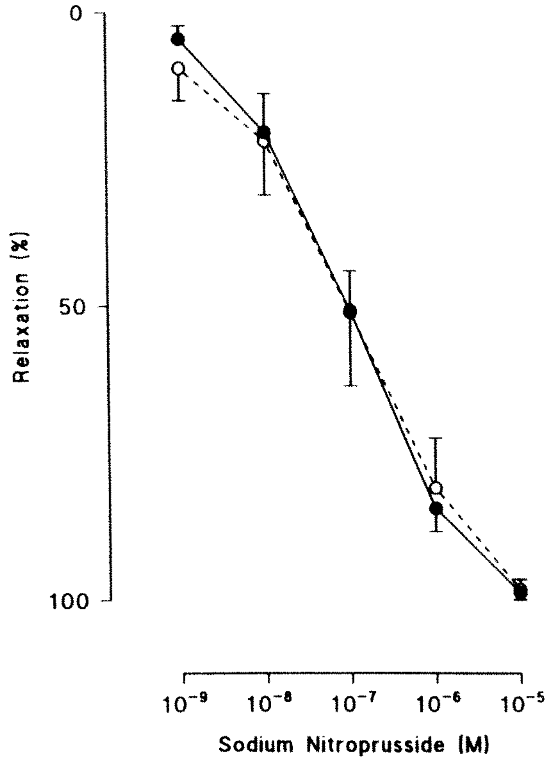

Fig 5. Relaxation response of internal mammary artery to sodium nitroprusside in control (●) and papaverine-treated (○) groups.

papaverine may account for the increase in blood flow shown in other studies [4]. The tenfold increase in blood flow reported in previous studies may be partly due to the reduced resistance produced by the vessel wall, causing the laminar flow to be enhanced [4]. However, some of the observed increase in blood flow may be due to the reduced resistance of the new vascular bed with a corresponding increase in "run off" to the arterial circulation of the heart. In the present study all control samples were removed from the distal end of the internal mammary artery before treatment with papaverine, and the treated segment was taken from the remaining length. It is known that the diameter of the internal mammary artery diminishes in a distal direction [17]; therefore, the differences in size between the control and treated groups may have been augmented by physiological differences. Because there is great variability of this phenomenon in patients it is impossible to estimate what influence this may have had. However, the increase in diameter is still greater than would have been anticipated from physiology alone.

The results of this study have shown that there can be variability in the contractile response of the internal mammary artery after intraluminal treatment with papaverine in that some vessels were unable to contract at all whereas others were able to produce strong contractions. The inability to produce smooth muscle contraction, caused by complete inhibition of the contractile machinery, may be related to the increase in diameter produced by papaverine. All three of the noncontracting vessels showed increases greater than the mean change. Two of the vessels that failed to contract showed increases of 45% and 43%, with the third increasing by 17%. Whether this variability is a factor of the effect of papaverine itself or caused by variation in exposure time could not be established by this study.

The results of this study refute the view that papaverine damages the endothelial cells of the internal mammary artery [6]. The discrepancy with other studies may be due to differences between cells in culture and cells in situ. In the natural state there is continual interaction between the smooth muscle, the endothelium, and the blood, with the endothelium acting as the interface between the other two.

In conclusion, this study has shown that the use of intraluminal papaverine increases the lumen of the internal mammary artery by 20%, contributing to the observed increase in blood flow and facilitating the surgical anastomosis. The contractile response to noradrenaline is significantly reduced after papaverine treatment. However, no impairment to endothelial-dependent relaxation was observed with either acetylcholine or bradykinin, and this study has refuted the suggestion that intraluminal papaverine may damage endothelial cells of the internal mammary artery when used during preparation for coronary artery bypass grafting.

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Notice From The Society of Thoracic Surgeons

New Abstract Deadline Date

The abstract due date is Monday, August 17, 1992, for all papers submitted for the Twenty-ninth Annual Meeting of The Society of Thoracic Surgeons, which will be held at the San Antonio Convention Center in San Antonio, Texas, January 25–27, 1993. No abstracts received after this date will be considered for presentation. The deadline for receipt of films and video tapes is Monday, August 3, 1992. Details are available in the Call for Abstracts published in this issue of *The Annals* or from Society headquarters, 401 N Michigan Avenue, Chicago, IL 60611 (telephone: (312) 644-6610).

Early and Late Outcome After Diagnostic Thoracoscopy and Talc Pleurodesis

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Although thoracoscopy is now recognized to be of both diagnostic and therapeutic value, the risks of this procedure have not been fully addressed. We retrospectively reviewed our experience with 100 patients who underwent 110 thoracoscopies during the period January 1989 to February 1991. Sixty-five men and 35 women (ratio of 1.9:1) underwent thoracoscopy using general anesthesia and intubation with a double-lumen endotracheal tube. The mean age was 64.2 ± 11.6 years (range, 13 to 85 years). The diagnosis was established in 48 (85.7%) of the 56 patients with undiagnosed pleural effusions. Forty-four patients were referred for therapeutic thoracoscopic talc pleurodesis. Pleurodesis was successful in 42 patients (95.5%). Four patients (4%) had five postoperative complications (two bronchopleural fistulas, two chest infections, and one arrhythmia). Five patients (5%) died after thoracoscopy; mean age was 67.8 ± 8.1 years (range, 55 to 77 years). The causes of death were cardiac arrest in 2, respiratory failure in 1, and malignant cachexia in 2. The findings of this study confirm that thoracoscopy can achieve high rates of diagnostic and therapeutic success but is not without attendant mortality in a high-risk patient population.

(Ann Thorac Surg 1992;53:1038–41)

Since the description of thoracoscopy by Jacobaeus in 1910 for the division of pleuropulmonary adhesions to achieve collapse of a tuberculous infected lung [1], the technique has become established as both a diagnostic and a therapeutic tool. Thoracoscopy has been employed for the removal of foreign bodies [2], in the assessment of thoracic trauma [3], and in the drainage of empyemas [2]. With this diversification in role, the number of thoracoscopic techniques has also increased. Thoracoscopy can now be done using a rigid or flexible scope under general or local anesthesia [4, 5]. However, because of the heterogeneity of reported techniques, identification of risk factors for morbidity and mortality associated with each method becomes difficult. Further, the long-term efficacy of talc pleurodesis in the clinical setting of malignant pleural effusions remains to be addressed.

We reviewed our series of 100 consecutive patients who underwent thoracoscopy in our unit over a 24-month period and analyzed our results, in particular any procedure-associated morbidity or mortality. A follow-up of patients who were discharged from the hospital after talc pleurodesis for malignant effusions was also done.

Material and Methods

One hundred patients underwent 110 thoracoscopies during the period January 1989 to February 1991 at Harefield Hospital. There were 65 men and 35 women (ratio of 1.9:1). The mean age was 64.2 ± 11.6 years. Fifty-six patients with pleural effusions were referred by respiratory physicians for the establishment of diagnoses after failure of primary investigations, including blind pleural biopsies or pleural aspirations or both. Ten of these patients underwent a second thoracoscopy during the same or second admission for therapeutic talc (hydrous magnesium sulfate) pleurodesis. Forty-four patients were referred for therapeutic talc pleurodesis. Of these 44 patients, 28 had pleural effusions (malignant in 26: mesothelioma in 2 and metastatic disease in 2; benign in 2: yellow nail syndrome in 1 and empyema in 1), 15 had pneumothoraces (emphysema/bullous disease in 14 and secondary to tuberculosis in 1), and 1 had a chylothorax resulting from advanced non-Hodgkin's lymphoma.

In all patients, thoracoscopy was performed under general anesthesia using a double-lumen endotracheal tube. Patients were placed in the lateral decubitus position, and the skin was prepared and draped as for a thoracotomy. A 2-cm incision was made in the fifth or sixth interspace, and air was introduced into the pleural cavity where a pneumothorax did not already exist. In patients with pleural effusion, needle aspiration was undertaken first to determine the location of the fluid; the thoracoscopy incision was then made over the aspiration site. A Storz rigid telescope (Karl Storz Endoscopy-America, Inc, Culver City, CA), was introduced through a 9-mm trocar. The pleural space was inspected, and any fluid aspirated was sent for cytological and bacteriological examination. Thoracoscopy was often assisted by single-lung anesthesia, and pleuropulmonary adhesions were broken down with biopsy forceps.

Before talc pleurodesis, a second trocar was inserted 5 to 7 cm anterior to the first to allow escape of insufflated gas. Talc (2 to 5 g) was insufflated until the whole pleural

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Table 1. Cause of Pleural Effusions in 56 Patients Undergoing Diagnostic Thoracoscopy

Cause	No. of Patients
Primary	
Mesothelioma	17[a]
Metastatic	
Breast	1
Lung	1
Pancreas	1
Adenocarcinoma (? primary site)	14
Squamous (? primary site)	4
Benign	
Tuberculosis	2
Pneumonia	2
Eosinophilic pleuritis	3
Cardiac failure	1
Liver cirrhosis	1
Primary biliary cirrhosis	1
Fibrosing alveolitis	1
Undetermined	7

[a] In 1 patient the diagnosis was made by minithoracotomy and open pleural biopsy.

cavity was seen to be coated on thoracoscopic examination. Both pleural and lung biopsies were performed when indicated, but in patients with undiagnosed large pleural effusions, pleurodesis was delayed until the diagnosis was established. The intercostal drain was positioned under direct vision of the thoracoscope using initially a needle to localize the area to be drained; this was particularly useful in patients with loculated pleural collections. After the drains had been positioned, the lung was fully expanded by positive-pressure ventilation to coapt the talc-covered parietal and visceral pleurae. Failure to fully expand the lung reduces the chances of achieving pleural symphysis.

Results

Group of 100 Patients

The diagnosis was established in 48 (85.7%) of the 56 patients with pleural effusions. The causative factors are listed in Table 1. In 7 patients the diagnosis remained undetermined. In 1 patient the thoracoscopic view was inadequate because of pleuropulmonary adhesions, and a minithoracotomy and pleural biopsy were performed. The diagnosis was mesothelioma. Ten patients underwent a second thoracoscopy for therapeutic talc pleurodesis during the same or second admission after establishment of the diagnosis. Talc pleurodesis was successful in all 10 of these patients and in 42 (95.5%) of the 44 patients referred for talc pleurodesis alone. Two patients required a second chemical pleurodesis with quinacrine hydrochloride through the intercostal tube on the third and fourth postoperative days. In both, poor lung expansion with positive-pressure ventilation had been noted at the time of thoracoscopy and was due to a fibrous visceral pleura.

The length of hospital stay was 6.0 ± 3.5 days (range, 2 to 23 days) for 85 patients undergoing a single procedure and 13 ± 7.7 days (range, 3 to 31 days) for 10 patients having two thoracoscopies. Four patients (4%) had complications. Postoperative chest infections developed in 2 patients, postoperative atrial fibrillation in 1 patient, and bronchopleural fistulas in 2 (1 of whom also had a chest infection). Both patients with bronchopleural fistula had undergone lung biopsy during thoracoscopy. These patients were managed successfully by prolonged drainage through the intercostal tube.

Five patients (5%) died after thoracoscopy: 3 with pleural effusions, 1 with pneumothorax, and 1 with hydropneumothorax (Table 2). Their mean age was 67.8 ± 8.1 years (range, 55 to 77 years), which was not significantly different ($p > 0.3$, nonpaired t test) from that of the group of patients who survived. The causes of death were cardiac arrest in 2 patients, respiratory failure in 1 patient, and malignant cachexia in 2. Of the 5 patients, 2 had severe chronic obstructive airway disease; the forced expiratory volume in 1 second to forced vital capacity ratios were 0.46 and 0.29. A third patient had mild chronic obstructive airway disease. No risk factors could be identified apart from advanced malignant disease in the other 2 patients. Postmortem examination was performed on 2 patients. Panlobular emphysema was found in the patient dying of respiratory failure, and cardiac failure without evidence of myocardial infarction was found in 1 of the patients who died of cardiac arrest.

Follow-up of Patients With Malignant Pleural Effusions or Chylothorax After Talc Pleurodesis

Thirty-seven patients who underwent successful talc pleurodesis for primary or metastatic malignancies of the pleural cavity were followed up after discharge from the hospital (range, 6 to 31 months). Thirty-six had pleural effusions, and 1 patient was treated for a chylothorax secondary to lymphoma. Seven of the 37 patients were lost to follow-up, but information pertaining to the remaining patients (81.1%) was available.

The mean survival was 17.7 weeks (range, 2 to 60 weeks). Twenty-three of the 30 patients had died, but 5 patients had survived 12 months or longer. One of these patients had a non-Hodgkin's lymphoma, 2 had metastatic carcinoma of the breast, and 2 had mesothelioma. Two patients required further treatment for recurrence of effusions after talc pleurodesis. Eighteen months after the initial pleurodesis, 1 patient with mesothelioma had reaccumulation of the effusion, which was successfully managed by insertion of a pleuroperitoneal shunt. He is alive and well 3 months after shunt insertion. In the second patient, who had a metastatic adenocarcinoma, dyspnea developed secondary to recurrence of the effusion 3 months after pleurodesis. This was managed by simple aspiration by his physician. The patient died 3 months later.

Comment

This study confirms the findings of previous authors [6, 7] that thoracoscopy can achieve a high diagnostic yield for

2. Summary of Data on Patients Who Died After Thoracoscopy

	Patient				
Variable	1	2	3	4	5
Age (y)	77	68	68	55	71
Sex	M	M	F	M	M
Indication	Pleural effusion	Pneumothorax	Pleural effusion	Pleural effusion	Hydropneumothorax
Risk factors	COAD, FEV_1/FVC 0.46, diabetes	COAD, FEV_1/FVC 0.29	Mild COAD	. . .	. . .
Procedure	Thoracoscopy and biopsy	Thoracoscopy and pleurodesis	Thoracoscopy and biopsy	Thoracoscopy and biopsy	Thoracoscopy and pleurodesis
Disease	Metastatic adenocarcinoma	Emphysema	Not established	Metastatic adenocarcinoma	Metastatic adenocarcinoma
Clinical cause of death	Cardiac arrest	Respiratory failure	Cardiac arrest	Malignant cachexia	Malignant cachexia
Autopsy	Not done	Panlobular emphysema	Cardiac failure	Not done	Not done

COAD = chronic obstructive airway disease; FEV_1/FVC = ratio of forced expiratory volume in 1 second to forced vital capacity.

pleural effusions and an equally high success rate for talc pleurodesis for pleural effusions or pneumothoraces. Further, the recurrence rate reported after talc pleurodesis for pneumothorax has been low. In a study of 241 patients followed up for up to 16.8 years, a mean recurrence rate of 6.6% was found [8]. This reflects the ability to visualize the whole pleural cavity with single-lung anesthesia and break down any pleuropulmonary adhesions under direct vision. Talc can then be delivered to the whole lung surface, ensuring the best chance of success. Performing the procedure under a general anesthetic not only permits excellent access but minimizes the pain to the patient from a chemical pleurodesis.

It is important to note that in both our patients in whom talc pleurodesis was unsuccessful, failure of the lung to expand fully with positive-pressure ventilation was recognized during thoracoscopy, a finding that has also been reported by others [7]. In both our patients, a second chemical pleurodesis was required and a limited basal pneumothorax accepted as the best result possible before discharge. Further, our results for patients with malignancies of the pleural cavity who had undergone talc pleurodesis also support the value of this technique in a group of terminally ill patients. Only 2 (6.7%) of the 30 patients who were followed up had recurrence of symptoms because of redevelopment of effusions.

Acute pneumonitis [9] and development of adult respiratory distress syndrome [10] have been documented in patients who had talc introduced into the pleural cavity as a suspension in normal saline solution, rather than talc insufflated as a powder. Of the 3 patients in whom adult respiratory distress syndrome developed within 72 hours of pleurodesis, 1 died. The possible pathogenesis remains unexplained, but there have been no further reports of this complication to date.

In younger patients with pneumothoraces, we prefer the technique of pleural abrasion combined with oversewing or stapling of any obvious bullae [11]. Pleural abrasion avoids the potential morbidity of pleurectomy and the uncertain long-term sequelae of talc pleurodesis in young patients with benign disease. Although talc poudrage has been associated with the development of mesothelioma from possible asbestos contamination of the talc, the link remains unproved [12]. Among 46 patients who had undergone talc pleurodesis and were followed up for 22 to 35 years, there were no cases of mesothelioma, and generalized pleural calcification and lung fibrosis developed in only 1 patient [13]. Nevertheless, the latent period for the development of pleural neoplasia after exposure to asbestos may be as long as 40 years [12]. There has also been some concern about performing talc pleurodesis in patients with benign disease, as respiratory function may be impaired. In the study by Lange and associates [13], only a mild restrictive defect was found 22 to 35 years after talc pleurodesis for spontaneous pneumothorax; the total lung capacity averaged 89% of the predicted value. However, like other authors, we do not recommend talc pleurodesis for patients who may be future candidates for lung or heart-lung transplantation.

To date, there has been a paucity of discussion in the literature as regards the complications after thoracoscopy; Table 3 provides the documented morbidity and mortality for patients who underwent thoracoscopy with general and local anesthesia. The development of surgical emphysema or bronchopleural fistula appears to be the most common complication. Both of our 2 patients who had a protracted air leak had undergone biopsy of lung that was covered in a thick visceral pleura infiltrated by metastatic carcinoma. In one of the largest series [16] to date, the incidence of clinically noticeable emphysema was 7%, which suggests that in most series this is probably an underreported complication. The risk of infection appears to be low, with only five infections recorded in a collected series of 1,145 patients (see Table 3); it is not our practice to administer prophylactic antibiotics to patients undergoing thoracoscopy. Patients with malignancies of the pleural cavity are at risk of development of tumor seeding at the site of the thoracoscopy incision, a finding present

Table 3. Complications After Thoracoscopy Reported in the Literature

Reference	No. of Patients	Morbidity	Mortality
General Anesthesia			
Daniel et al, 1990 [7]	40 (and 38 with general and 2 with local anesthesia)	Bronchopleural fistulas (2)	2 (5%): pulmonary embolus, advanced lymphoma
Weissberg et al, 1980 [14]	73	Subcutaneous emphysema (2)	None
Ohri et al, 1992 [present series]	100	Chest infection (2), bronchopleural fistulas (2), arrhythmia (1)	5 (5%) (see Table 2)
Local Anesthesia			
Davidson et al, 1988 [15]	30	Tumor seeding at thoracoscopy site (2)	. . .
Enk and Viskum, 1981 [16]	566	Air embolism during insufflation (1), vasovagal attacks (2), emphysema (36)	. . .
Boutin et al, 1981 [17]	215	Intrapleural hemorrhage (1), subcutaneous emphysema (2), empyema (1), cardiac ischemia (1), tumor seeding at thoracoscopy site (6)	5 (2.3%): advanced malignancies
DeCamp et al, 1973 [18]	121	"Minimal air leak hypotension" (6), empyema (1)	. . .

in 6 of 215 patients discussed by Boutin and colleagues [17]. In a smaller series in which 2 of 30 patients had this problem, it was successfully palliated with radiotherapy [15]. Including the present series, we could find only three reported deaths after thoracoscopy. In the series of Boutin and co-workers [17], five deaths (2.3%) were recorded within 30 days of thoracoscopy. However, the authors stated that death was not due to thoracoscopy but to advanced disease. In our patients, advanced malignant disease was the only identifiable risk factor in 2 patients, but it was probably contributory to the death of another 1 of the remaining 3 patients who died.

Patients with advanced malignancy are often malnourished with coexisting disease in other organ systems, a finding reflected in the long hospital stay after talc poudrage. This underscores the importance of patient selection for a group often containing terminally ill patients. There would appear to be little advantage in undertaking thoracoscopy with definite, albeit low risks of morbidity and mortality for a patient who has a very limited life expectancy, substantially compromised cardiorespiratory reserve, or both. In such patients, pleural effusions or pneumothoraces are best treated by repeated aspiration or tube drainage.

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Completion Pneumonectomy After Bronchial Sleeve Resection: Incidence, Indications, and Results

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During the years 1960 through 1989, 145 patients underwent sleeve lobectomy or sleeve resection of a main bronchus. Completion pneumonectomy was performed in 19 patients (13.1%). Indications were bronchostenosis without malignancy in 10 patients, positive resection margins in 3, recurrent tumor in 5, and anastomotic dehiscence in 1. Mean age at sleeve operation was 59.3 years. In 18 patients the histology was squamous cell carcinoma and in 1 patient, carcinoid tumor. The mean interval between sleeve resection and completion pneumonectomy was 5.7 months (range, 3 to 16 months) for the patients with stenosis and 6.6 months (range, 1 to 17 months) for the others. There were 3 operative deaths (15.8%). The mean follow-up was 53.2 months. Five-year and 10-year survival rates after completion pneumonectomy for the patients with stenosis were 54% and 41%, respectively, and for the others, 52% and 52%.

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Sleeve resection has proved to be an adequate operation for lung cancer and is an alternative to pneumonectomy in select patients with bronchogenic carcinoma [1]. It is a valuable method to preserve functional lung tissue, and patients in whom a second primary cancer develops may benefit from a second resection.

Contrary to standard resectional procedures, an end-to-end bronchial anastomosis is performed in full sleeve resections. This may cause anastomotic complications that eventually necessitate completion pneumonectomy [2], the incidence of which has been infrequently reported. The incidence and indications for completion pneumonectomy were studied in a series of 145 patients who underwent full bronchial sleeve resection. Mean follow-up after sleeve resection was 47.9 months (maximum follow-up, 223 months). The results and long-term survival according to the specific indication are discussed.

Material and Methods

During the years 1960 through 1989, 145 patients underwent full bronchial sleeve lobectomy or sleeve resection of a main bronchus, which represents our total experience with bronchial sleeve resection. Follow-up was complete except for 1 patient, who was lost to follow-up 4 years after operation. Morbidity, mortality, and long-term survival after sleeve resection were reported previously [3].

In total, 19 patients (13.1%), all men, underwent completion pneumonectomy. A benign bronchostenosis was found as a late postoperative complication after sleeve resection in 13 patients (8.9%). In 3 of them, bronchoscopic dilation was successful; in 10, completion pneumonectomy was eventually performed. Three patients had positive resection margins at definitive pathological examination and underwent completion pneumonectomy within several weeks after the original sleeve resection; all were operated on before 1980. Five patients had recurrent tumor (Table 1): 4 had negative resection margins and 1, carcinoma in situ at the initial operation (patient 5). One patient had anastomotic dehiscence and underwent completion pneumonectomy 6 days after sleeve right upper lobectomy. During the original operation, purulent secretions were noted in the reimplanted middle and lower lobes.

Mean age at sleeve operation was 59.3 ± 9.3 years (range, 27 to 71 years). Sixteen patients initially had a sleeve resection of the right upper lobe; 1 patient, a sleeve lobectomy of the right upper and middle lobes; and 2 patients, a left upper sleeve lobectomy. The histology was squamous cell carcinoma in 18 patients and carcinoid tumor in 1 patient. The mean interval between sleeve operation and completion pneumonectomy was 5.7 months (range, 3 to 16 months) for the patients with bronchostenosis and 6.6 months (range, 1 to 17 months) for the others.

Follow-up data were obtained from a questionnaire sent to the referring pulmonary physicians or from the records of the patients followed up in our institution.

Actuarial survival curves were calculated according to the Kaplan-Meier method. Difference in survival was assessed by the Tarone-Ware test using BMDP statistical software (Los Angeles, CA, 1990). Comparison between qualitative data was made with the χ^2 test (with Yates' continuity correction when necessary).

Results

The main indication for completion pneumonectomy was stenosis of the bronchial anastomosis without recurrent tumor in 10 patients. In 4 of them, polypropylene

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Table 1. Characteristics of Patients With Recurrent Tumor

Patient No.	Initial Tumor		Histology	Interval (mo)	Recurrent Tumor	
	TNM	Stage			TNM	Stage
1	T2 N1 M0	II	Squamous cell carcinoma	2	T4 N1 M0	IIIb
2	T2 N0 M0	I	Squamous cell carcinoma	12	T3 N0 M0	IIIa
3	T2 N1 M0	II	Squamous cell carcinoma	17	T3 N0 M0	IIIa
4	T2 N1 M0	II	Squamous cell carcinoma	8	T2 N0 M0	I
5[a]	T2 N0 M0	I	Squamous cell carcinoma	15	T3 N0 M0	IIIa

[a] In this patient, carcinoma in situ was found at the resection margin during sleeve operation.

(Prolene) or Teflon-coated polyester (Tevdek) had been used as the suture material, and a continuous suture, interrupted and knotted at three places 120 degrees apart, had been performed. In the 6 other patients, interrupted polyglactin (Vicryl) sutures had been used for the cartilaginous part of the anastomosis and continuous polypropylene (Prolene) for the membranous part.

In total, continuous polypropylene or Teflon-coated polyester sutures had been used in 28 patients, seen mainly before 1980. In this group, the incidence of completion pneumonectomy for bronchostenosis was 14.3% (4/28). In 105 sleeve resections, interrupted polyglactin sutures had been used, and the incidence of completion pneumonectomy for bronchostenosis was 5.7% (6/105). However, this difference was not significant ($p > 0.25$).

The operative mortality rate for completion pneumonectomy was 15.8% (3 patients). Two patients died of cardiac-related causes (myocardial infarction and ventricular fibrillation) and 1 of a fistula of the bronchial stump 4 days after completion pneumonectomy. The major postoperative complication was a bronchopleural fistula in 1 patient. It was treated by fenestration and secondary closure with omental transposition. This patient is doing well 9 months after completion pneumonectomy.

All survival and follow-up data include operative mortality. The mean follow-up after completion pneumonectomy for the 19 patients was 53.2 months. Maximum follow-up was 221 months. Six patients died during follow-up. The mean interval between completion pneumonectomy and death was 39.8 months (range, 3 to 105 months). Causes of late death were local recurrence in 1 patient, distant metastases in 2 patients, cardiac-related cause in 1, respiratory insufficiency in 1, and unknown in 1 patient.

Ten patients are alive without signs of local recurrence or metastases after a mean follow-up of 77.1 months (range, 2 to 221 months). Five-year and 10-year survival rates after completion pneumonectomy for the 19 patients were 0.47 ± 0.14 and 0.38 ± 0.14, respectively (Fig 1). For the 10 patients undergoing completion pneumonectomy because of bronchostenosis, 5-year and 10-year survival rates were 0.54 ± 0.14 and 0.41 ± 0.17, respectively, and for the 9 others, 0.52 ± 0.18 and 0.52 ± 0.18 (Fig 2). The difference in survival between these two groups was not significant ($p = 0.24$).

Comment

In recent years, bronchial sleeve resection has proved to be an adequate operation for lung cancer and is an alternative to pneumonectomy for select types of bronchogenic carcinoma, mostly centrally located squamous cell carcinoma [1]. Functional lung tissue is preserved, and this not only improves the quality of life [4] but may allow a subsequent resection in patients with development of a second primary lung cancer, the incidence of which has increased in recent years [5].

However, in sleeve or wedge resections, a full or partial bronchial anastomosis is created. This can cause additional complications not encountered in standard resectional procedures [2]. In the so-called full sleeve resection, a portion of the main bronchus is removed with an end-to-end anastomosis of the remaining bronchial stump in the main bronchus. In this procedure, the bronchial arteries are usually completely interrupted, which can result in poor healing of the anastomosis.

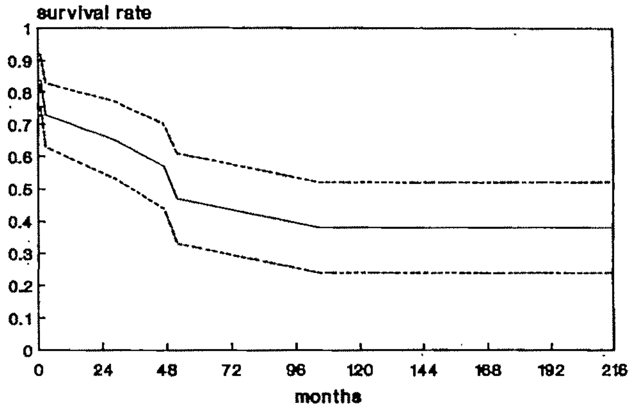

Fig 1. Actuarial survival curve with standard deviation (broken lines) *for the 19 patients who underwent completion pneumonectomy.*

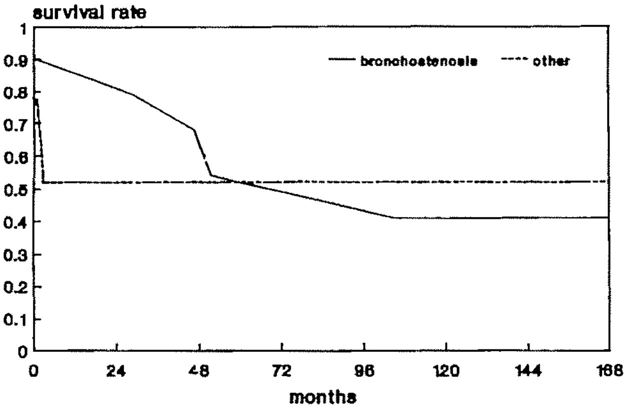

Fig 2. Actuarial survival curves by indication for completion pneumonectomy: 10 patients with benign bronchostenosis and 9 patients with other indications.

In a canine experimental model [6] of lung reimplantation with complete interruption of the bronchial arteries, a network of many fine arterial channels across the anastomosis could be demonstrated by selective bronchial arteriography within 3 weeks of reimplantation. Reestablishment of distal bronchial arterial flow occurred within 4 weeks of bronchial artery division.

Whether it is necessary to cover the bronchial anastomosis with some viable tissue to reduce ischemic complications after sleeve resection remains controversial [7]. In dogs, a pedicled pleural wrap did not significantly improve bronchial circulation [8].

As most sleeve resections are performed for centrally located bronchial tumors, residual malignant cells at the suture line can give rise to early recurrence. This underscores the necessity for careful frozen-section examination of the bronchial margins before the anastomosis is made [7].

These anastomotic complications after sleeve resection can eventually necessitate completion pneumonectomy, the incidence of which has been infrequently reported. In a series of 43 patients who underwent sleeve resection for different types of bronchial tumors, Huidekoper and van Ginneken [9] mentioned 2 patients with late complications, one of which was a bronchial stenosis requiring completion pneumonectomy. Faber and colleagues [1, 10] described their experience with 118 sleeve lobectomies. Completion pneumonectomy was performed in 8 patients (6.8%) without operative mortality. Indications were mainly anastomotic complications, ie, stenosis and dehiscence, in 6 patients, 4 of whom had received preoperative radiotherapy. The indication for completion pneumonectomy was residual tumor at the resection margin in 1 patient and recurrent tumor 16 months after sleeve lobectomy in another.

Watanabe and associates [4] presented a series of 76 bronchoplastic procedures for bronchogenic carcinoma without carinal involvement. One patient required completion pneumonectomy because of thrombosis of the pulmonary artery after sleeve left upper lobectomy with sleeve resection of the pulmonary artery, a so-called double-sleeve resection.

In our series of 145 patients who underwent full bronchial sleeve resection, completion pneumonectomy was necessary in 19 (13.1%), none of whom had received preoperative radiotherapy. The main indications were benign bronchostenosis and locally recurrent tumor. Five-year and 10-year survival rates after completion pneumonectomy were 0.47 and 0.38 with no difference in survival according to the specific indication for completion pneumonectomy. The mean interval between sleeve resection and completion pneumonectomy was relatively short, 5.7 months for the patients with stenosis and 6.6 months for the others.

Regarding suture material for the bronchial anastomosis, absorbable suture was found to be superior to nonabsorbable suture in growing puppies [11]. Absorbable sutures are also mainly used in humans [4, 7, 12]. In our series, the incidence of bronchial stenosis necessitating completion pneumonectomy was 14.3% when nonabsorbable polypropylene or Teflon-coated polyester was used as the suture material versus 5.7% when absorbable polyglactin was used. However, this difference was not significant.

After sleeve resection, repeat bronchoscopy is necessary to aspirate secretions, remove granulation tissue, and take biopsy specimens from the region of the anastomosis when suspicious tissue is found. In the case of stenosis of the bronchial anastomosis without recurrent tumor, bronchoscopic dilation is attempted. If this is not successful and persistent problems of atelectasis, infection, or suppuration of the remaining lobe or lobes exist, a completion pneumonectomy is eventually performed.

In a recent report [13], 113 patients underwent completion pneumonectomy after various operations, but none had an initial sleeve resection. The overall operative mortality rate was 12.4%. Patients were divided into three groups according to the specific indication for completion pneumonectomy. In 64 patients, the indication was lung cancer. The operative mortality rate in this group was 9.4% with a 5-year survival rate of 26.4%. The indication was pulmonary metastases in 20 patients. They underwent reoperation with no operative mortality and a 5-year survival rate of 40.8%. In 29 patients, the indication was a benign condition, including bronchial stenosis in 3. In this group, the operative mortality rate was 27.6%, and 55.2% had major complications related to an extensive inflammatory process found during operation; the 5-year survival rate was 27.2%.

In our series of 19 patients, the overall operative mortality rate was 15.8%. In 10 patients (52.6%), the indication for completion pneumonectomy was benign bronchostenosis. In this group, 1 patient died postoperatively of cardiac arrhythmia and ventricular fibrillation, giving an operative mortality rate of 10% for benign conditions.

Deslauriers [14] pointed out that completion pneumonectomy is a technically difficult procedure that must be done by an experienced surgeon. The intrapleural plane should be followed as closely as possible during dissection. When the intrapericardial cavity has not been obliterated by previous radiotherapy or inflammation, intrapericardial vascular control is often helpful. Reinforcement of the bronchial stump with viable tissue should be attempted to minimize postoperative stump complications.

In conclusion, in our series of 145 patients who underwent sleeve resection, completion pneumonectomy was necessary in 19 (13.1%). Frozen-section examination of the bronchial resection margins during sleeve operation is mandatory to obtain adequate tumor clearance. After sleeve resection, regular bronchoscopic control is necessary to detect early recurrent tumor or anastomotic complications and to treat them accordingly.

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Twenty-Four-Hour Heparin-Free Veno–Right Ventricular ECMO: An Experimental Study

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Platelets and coagulation factors were studied during 24-hour heparin-free veno–right ventricular extracorporeal membrane oxygenation (ECMO) in 6 healthy pigs. An endpoint attached and covalently bonded heparin-coated ECMO system was used in these experiments. The veno–right ventricular ECMO supplied the total lung function of the animals, and after 24 hours, all the animals were successfully weaned from ECMO. Lung function and central hemodynamics were not affected by the procedure. Because all the animals showed a significant reduction in plasma volume, the concentration of measured coagulation variables was corrected both for plasma volume changes and for hemodilution. The platelet count and the plasma-free hemoglobin level were not significantly altered by ECMO. Similarly, the prothrombin complex, antithrombin, thrombin-antithrombin complex, factor XII, and the urinary excretion of 2,3-dinor-thromboxane B_2 were not significantly altered. Fibrinogen and fibrin monomer increased significantly, whereas von Willebrand factor was significantly decreased after ECMO. In summary, 24-hour heparin-free veno–right ventricular total extracorporeal lung assistance does not affect the platelets and the coagulation system significantly in healthy juvenile pigs.

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Our group [1] has described heparin-free veno–right ventricular bypass as a substitute for total lung function. In this method, oxygenation of the blood is achieved by draining venous blood from the right atrium and caval veins into an oxygenator and returning the oxygenated blood to the right ventricle. Recirculation of the oxygenated blood into the extracorporeal circuit is thereby restricted to the minimum possible. The efficacy of this bypass technique was demonstrated clinically for the first time on a 20-year-old man with posttraumatic adult respiratory distress syndrome [2]. The patient was successfully weaned from bypass after 35 days. During the period of extracorporeal membrane oxygenation (ECMO), disseminated intravascular coagulation developed, and treatment with low-dose systemic heparin sodium was omitted during the last 24 days of ECMO.

The aim of the present study was to investigate whether heparin-free veno–right ventricular ECMO per se disturbs the platelet function and the coagulation cascade significantly.

Material and Methods

Six Swedish native-breed male pigs with a mean weight of 60 kg (range, 56 to 68 kg) were selected for this study. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

The animals were put to sleep by intramuscular injection of ketamine hydrochloride (Ketalar; Parke-Davis, Morris Plains, NJ), 40 mg/kg of body weight. Sodium thiopental (Pentothal Natrium; Abbott Laboratories, North Chicago, IL), 250 to 500 mg, was administered intravenously before a tracheostomy was done, and a No. 7 endotracheal tube was placed in the trachea and connected to a Servoventilator 900 (Siemens-Elema AB, Stockholm, Sweden). Volume-controlled ventilation with an inspired oxygen fraction of 0.4 and a minute ventilation of 170 mL/kg was instituted. Anesthesia and relaxation were maintained with continuous intravenous infusion of a mixture of Ketalar, 300 mg/h, and pancuronium bromide (Pavulon; Organon Teknika, Boxtel, the Netherlands), 20 mg/h, dissolved in 10% glucose. Central venous and aortic pressure lines were established through the neck vessels. An indwelling Foley catheter was placed in the urinary bladder through a suprapubic cystotomy. Prophylactic antibiotics (penicillin and streptomycin sulfate) were given every 12 hours. Four liters of intravenous fluids (glucose 10%, 2 L; albumin 5%, 1 L; and Ringer's acetate, 1 L) was provided over the 24-hour period. Balanced isotonic solution (2.5% glucose and 0.45% sodium chloride) was also given to compensate for the urinary losses.

The chest was entered through a midline sternotomy, and pulmonary artery and left atrial pressure lines were established. Cardiac output was continuously recorded by an electromagnetic flow probe placed over the ascending aorta (45-mm Cliniflow 601D; Carolina Medical Electronics, Winston-Salem, NC). Cardiac output also was mea-

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sured with the Swan-Ganz thermodilution technique (Baxter Healthcare Corporation, Irvine, CA) on two occasions in each animal. Three pursestring sutures were placed over the right atrium for venous and right ventricular cannulation. A 24F wire-reinforced cannula was then guided into the right ventricle (across the tricuspid valve) under continuous pressure manometry for arterial return from the ECMO system. Venous drainage into the ECMO system was provided by two 28F wire-reinforced cannulas, one placed in the right atrium and the other in the inferior vena cava. Veno–right ventricular bypass was established, and the maximum possible blood flow was diverted into the ECMO system.

The ECMO system used for bypass comprised a Maxima membrane oxygenator (Medtronic, Inc, Anaheim, CA), wire-reinforced cannulas (Research Medical Inc, Salt Lake City, UT), an in-line venous collapsible balloon and its servoregulator (Carmeda AB, Stockholm, Sweden), and polyvinyl chloride tubing and connectors, all heparin coated (Carmeda AB). The total surface area of the system including the cannulas was about 2 m^2. A roller pump and a hypo-hyperthermia machine (Gambro, Lund, Sweden) were used in the extracorporeal bypass circuit. The ECMO system was primed with 970 mL of 5% albumin. No local or systemic heparin was administered to the animals or put into the ECMO system during the 24-hour bypass period.

The oxygenators were run on 100% oxygen, and the blood/oxygen gas ratio was maintained at 1:1. Once stable bypass was achieved, the ventilator was reset to a dead-space ventilation (minute volume, 1 L; frequency, 20/min; positive end-expiratory pressure, 5 cm H_2O; and inspired oxygen fraction, 0.21), enough to hold the lungs in a slightly expanded state but not enough to contribute to oxygenation or carbon dioxide removal, ie, the blood gases in the pulmonary artery, left atrium and aorta did not differ significantly. The rectal temperature of the animals was maintained between 37.0° and 38°C.

After 24 hours of ECMO, the lungs were ventilated again in the same manner as before the initiation of ECMO, and then heparin, 3 mg/kg, was administered intravenously. The animal was sacrificed, and postmortem examination of the lungs, heart, liver, and kidneys was performed. The pulmonary arteries were meticulously dissected and examined for thromboemboli. The blood in the extracorporeal circuit was drained and the residual blood washed with 5 L of normal saline solution. The ECMO system was examined for clot formation and tube damage. The animal was weighed again after the conclusion of the experiment.

The plasma volume of the animal was measured by a radioisotope technique using iodine 125-labeled human serum albumin, 0.03 MBq/20 kg. The dilution of the radioactivity was followed for 30 minutes. At the end of ECMO, plasma volume was again measured by the same method, but a higher dose of isotope was administered. Baseline radioactivity in the blood was measured on both occasions.

Monitoring

The following vital signs were monitored on an hourly basis: heart rate, aortic pressure, central venous pressure, pulmonary artery and left atrial pressures, cardiac output, urinary output, rectal temperature, systemic arterial and venous oxygen and carbon dioxide tensions, systemic arterial blood pH and base excess, blood flow and oxygen gas flow rates through the oxygenator, and gas analysis of blood leaving the oxygenator. Hemoglobin, hematocrit, plasma-free hemoglobin, serum osmolality, and serum electrolytes were measured and routine renal and liver function tests done before and after ECMO.

Blood Platelet and Coagulation Studies

Platelet count was performed in an electronic cell counter (Coulter S 880; Coulter Electronics, Luton, England). Activated clotting time was determined using a Hemochron 400 (International Technidyne Corp, Edison, NJ). Tests for prothrombin complex (Nycotest) and activated partial thromboplastin time (Cephotest) were performed according to the manufacturer's instructions (Nycomed AS, Oslo, Norway). Antithrombin was determined by a functional chromogenic assay [3]. Thrombin-antithrombin complexes were measured by an enzyme-linked immunosorbent assay [4] by means of kits (Enzygnost-TAT; Behring, Marburg/Lahn, Germany). Fibrinogen was measured by a polymerization-time determination [5]. Fibrin monomers were determined enzymatically (Coa set; Kabi Pharmacia, Stockholm, Sweden) [6]. Factor XII was measured by a chromogenic assay [7]. The von Willebrand factor was determined in an enzyme-linked immunosorbent assay system [8].

Plasma levels of antithrombin and factor XII were measured by employing pooled porcine plasma as the calibration standard, whereas plasma levels of thrombin-antithrombin complex, fibrin monomer, and von Willebrand factor were measured using antibodies against the human proteins and human calibration standards.

The in vivo formation of thromboxane A_2 was monitored by mass spectrometric measurement of its metabolite 2,3-dinor-thromboxane B_2 (2,3-dinor-TxB_2) in urine [9]. Urine already present in the urinary bladder before the start of the experiment was saved separately from that collected before the initiation of ECMO and the 6-hour samples collected during the 24-hour ECMO period (six samples). The urine samples were refrigerated at −20°C until analyzed.

Statistical Analysis

Wilcoxon's signed-rank test for paired data was used to determine the significance of difference in the variables measured before and 24 hours after ECMO. A p value of less than 0.05 was considered significant.

Results

Clinical Variables

During the 24 hours of veno–right ventricular ECMO and the following period, all the animals maintained stable

Table 1. Respiratory Variables Before and 24 Hours After Veno–Right Ventricular ECMO[a]

Time	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	pH	Base Excess (mmol/L)	MPAP (mm Hg)	PVR[b] ($dyn \cdot s^{-1} \cdot cm^{-5}$)
Before ECMO	171 ± 10	35 ± 2	7.54 ± 0.02	6.8 ± 1.0	21.6 ± 1.2	291 ± 72
After ECMO	114 ± 23	33 ± 2	7.54 ± 0.02	4.7 ± 0.9	21.2 ± 1.4	321 ± 106

[a] Data are shown as the mean ± the standard error of the mean for 6 pigs. [b] Data are from 4 pigs.

ECMO = extracorporeal membrane oxygenation; MPAP = mean pulmonary artery pressure; $PaCO_2$ = arterial carbon dioxide tension; PaO_2 = arterial oxygen tension; PVR = pulmonary vascular resistance.

systemic and pulmonary hemodynamics (Table 1). The mean extracorporeal blood flow rate amounted to about 80% of the mean systemic cardiac output (5 L). The systemic arterial and the mixed venous blood gas analyses during and after ECMO were also within normal limits (see Table 1). Bleeding from the open sternotomy wound and from the cardiac cannulation sites was negligible, and no exogenous blood transfusion was given. Routine liver and renal function test results remained essentially unaltered after 24 hours of ECMO. Both plasma and blood volume measurements showed a significant decrease (11% and 15%, respectively) after 24 hours of ECMO (Table 2). All the animals had a significant weight gain because of fluid retention, and the serum osmolality showed a significant decrease (see Table 2). Urine samples showed no macroscopic hemolysis, and the plasma-free hemoglobin levels remained within normal limits.

After the onset of ECMO, there was an immediate decrease in both the hematocrit and the hemoglobin concentration because of hemodilution; thereafter neither variable showed a significant change (Fig 1). After 24 hours of ECMO, the total hemoglobin in the blood had decreased by about 35% ($p < 0.05$), and after correction for hemodilution, the decrease was about 15% (p = not significant) (see Table 2). The mean hemoglobin concentration in the suction bottles (as a measure of blood loss during the 24-hour ECMO period) at the end of the experiment in 3 animals was 24 g (range, 12 to 42 g), 5% of the mean preoperative total hemoglobin.

All the oxygenators functioned satisfactorily, and none of them had a plasma leak. At the conclusion of the experiments, all the oxygenators showed small, sporadic but definite areas of thrombosis with special affinity for areas of blood stagnation. The conduit portion of the ECMO system, however, was devoid of these macroscopic deposits.

At postmortem examination, there was no evidence of macroscopic thrombosis in the heart or pulmonary artery branches, nor was there any suggestion of pulmonary embolism. The liver and the kidneys looked normal.

Coagulation Variables

The results are shown in Figures 1 and 2 and in Table 3. When the measured levels of the coagulation factors were corrected for blood loss in the respective animal, only fibrinogen, fibrin monomer, and von Willebrand factor were significantly affected by the 24 hours of ECMO. The urinary levels of 2,3-dinor-TxB_2 increased significantly in the period preceding ECMO. After the initiation of ECMO, these levels decreased successively, and in the last 6 hours of ECMO, they were similar to those in the period before the experiment.

Comment

The veno–right ventricular ECMO used in this study served as total extracorporeal lung assistance over a period of 24 hours, and about 80% of the total cardiac output circulated through the extracorporeal circuit during this period (for further details see [1]). During veno–right ventricular ECMO, the lung is the only organ likely to be affected by eventual embolization from the extracorporeal circuit. In the present study, no macroscopic pulmonary artery thrombosis or embolization was seen in any of the animals, and the lungs appeared normal. This finding together with normal arterial oxygen and carbon dioxide tensions and normal pulmonary vascular resistance after ECMO suggests no significant thrombosis or embolization in the lungs during the 24-hour heparin-free ECMO.

The amount of bleeding from the open sternotomy wound ought to serve as in vivo evidence of the efficiency

Table 2. Body Fluid Dynamics Before and 24 Hours After Veno–Right Ventricular ECMO[a,b]

Time	Blood Volume (L)	Plasma Volume (L)	Total hemoglobin (g)	Serum osmolality (mosm/kg)	Body Weight (kg)
Before ECMO	3.9 ± 0.07	2.7 ± 0.08	439 ± 26	294 ± 1	60.3 ± 2.0
After ECMO	3.3 ± 0.09[c]	2.4 ± 0.10[c]	289 ± 11[c] (375 ± 14)[d]	279 ± 4[c]	64.6 ± 2.3[c]

[a] Data are shown as the mean ± the standard error of the mean for 6 pigs. [b] The positive fluid balance after 24-hour ECMO was 5.7 ± 0.5 L (n = 6). [c] Significance: $p < 0.05$. [d] This is the value after correction for hemoglobin loss in the ECMO system.

ECMO = extracorporeal membrane oxygenation.

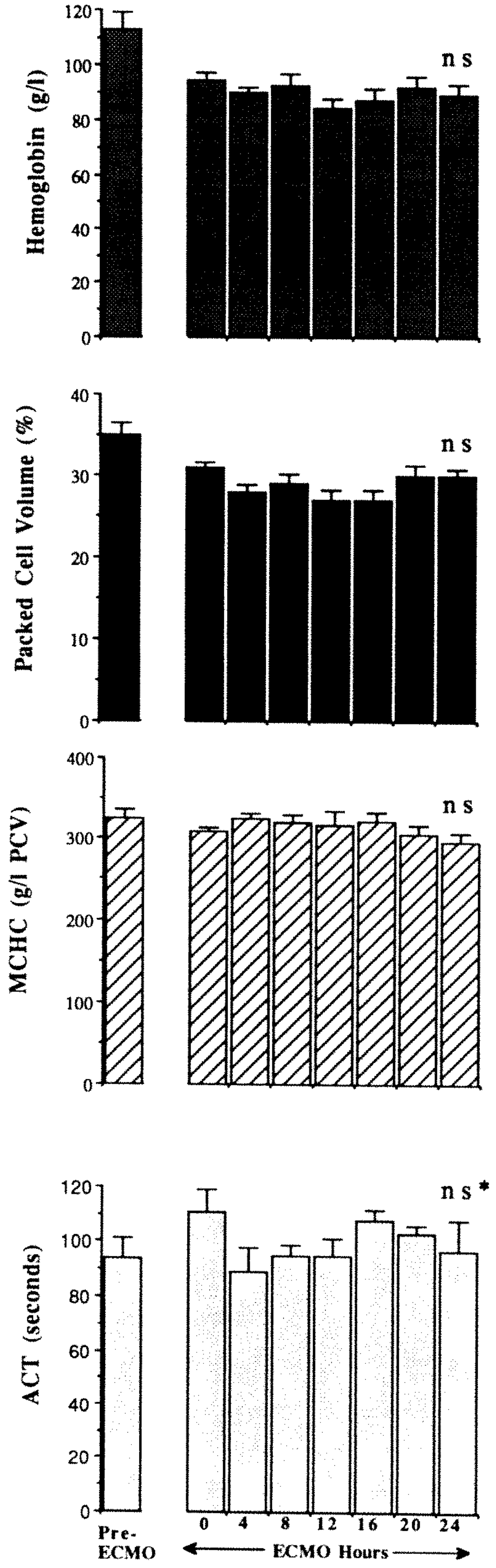

Fig 1. Hemoglobin value, packed cell volume (PCV), *mean cell hemoglobin concentration* (MCHC), *and activated clotting time* (ACT) *during 24 hours of extracorporeal membrane oxygenation* (ECMO). (ns = *not significant versus value at 0 ECMO hour;* ns* = *not significant versus pre-ECMO value.)*

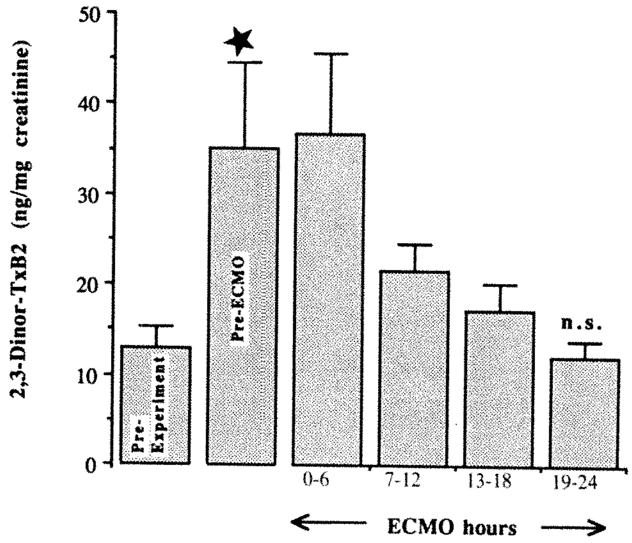

Fig 2. Urinary excretion of 2,3-dinor-thromboxane B_2 before and during the experiment. (★ = $p < 0.05$, *versus preexperiment value;* n.s. = *not significant versus preexperiment value.)*

of the circulating platelets and the coagulation factors. In these experiments, there was loss of about 15% of the total hemoglobin during the 24-hour ECMO period, and about a third (5%) of this was lost through bleeding during the performance of the sternotomy and cannulations. Most of

Table 3. Coagulation Profile Before and 24 Hours After Veno–Right Ventricular ECMO[a]

Variable	Before ECMO	After ECMO	Correction After ECMO[b]
APTT (s)	23	23	. . .
PT (%)	106 ± 22	105 ± 12	. . .
Total platelets (×10^9)	1,411 ± 159	1,178 ± 160	1,728 ± 167
Total antithrombin III (U)	2,783 ± 144	1,493 ± 115[a]	2,244 ± 121
Total thrombin-antithrombin complex (μg)	40.09 ± 10.71	40.52 ± 6.48	61.13 ± 9.32
Total fibin monomer (nmol)	491.63 ± 24.65	897 ± 65[c]	1,372 ± 140[c]
Total fibrinogen (g)	3.56 ± 0.42	5.72 ± 0.23	8.73 ± 0.63[c]
Total factor XII (U)	2,077 ± 131	1,329 ± 123[c]	1,995 ± 160
Total von Willebrand factor (IU)	4,043 ± 636	1,242 ± 205[c,d]	1,862 ± 195[c,d]

[a] Data are expressed in absolute values and, where applicable, are shown as the mean ± the standard error of the mean for 6 pigs. [b] This shows the values after correction for the blood lost at the end of ECMO. [c] Significance: $p < 0.05$. [d] Data are for 5 pigs.

APTT = activated partial thromboplastin time; ECMO = extracorporeal membrane oxygenation; PT = prothrombin complex.

the remaining loss was due to the frequent blood sampling during the 24-hour observation period. No bleeding was observed from the open sternotomy wound or the cannulation sites during or after the ECMO period. Because the hemoglobin and hematocrit values also remained essentially unaltered after the initiation of ECMO, serious dysfunction of the platelets and coagulation factors is unlikely.

After conventional cardiopulmonary bypass, there is loss of fluids from the intravascular compartment leading to an increase in the volume of the interstitial fluids and a reduction in the plasma volume [10]. The magnitude of the increase in extracellular fluid volume is directly related to the duration of bypass [11]. In the present study, a significant reduction in both the blood and plasma volumes was observed. Under these circumstances, we thought it appropriate that all the blood and plasma variables including hemoglobin and platelets be presented as total values. For all immunochemical determinations, cross-reactivity between porcine proteins and antibodies toward human proteins was used. Therefore, the values obtained may not reflect the true plasma concentration of the given protein. On the other hand, a comparison of the values obtained over time in the animals is likely to represent the true change in the given variable.

Unaltered values of antithrombin, factor XII, thrombin-antithrombin complex, activated partial thromboplastin time, and prothrombin complex are suggestive of no major activation of the coagulation cascade. The significant elevation of fibrin monomer may be explained by the sporadic clot formation in the membrane oxygenators. The significant increase in plasma fibrinogen is suggestive of an inflammatory reaction. Fibrinogen levels do increase after a major operation [12] and represent an acute-phase reaction. The significant reduction in the levels of von Willebrand factor was unexpected, and we have no explanation for it.

Levels of the thrombin-antithrombin complex and fibrin monomer were higher before ECMO than the expected normal, and so was the urinary excretion of 2,3-dinor-TxB_2. It appears that the sternotomy procedure is enough to activate both these systems substantially. Under these circumstances, the progressive decrease in the urinary excretion of 2,3-dinor-TxB_2 after the first 6 hours of ECMO suggests that the heparin-coated surface in question did not perpetuate the activation and the release of thromboxane A_2 from the platelets.

Thromboxane A_2 is chemically unstable and is rapidly hydrolyzed to TxB_2. Estimation of plasma TxB_2 levels is fraught with error, as this compound may be formed rapidly and in large quantities during sample collection and processing procedures [13]. Studies [14] of urinary excretion of 2,3-dinor-TxB_2 in humans indicate that this metabolite is a good indicator of the in vivo synthesis of thromboxane A_2. Surface-induced activation of platelets leads to both the aggregation and the release reaction coupled with the formation of thromboxane A_2 [15, 16], and the alterations in the in vivo synthesis of thromboxane A_2 are reflected by a change in the excretion of its urinary metabolites within 1 hour [17]. Therefore, measurement of urinary 2,3-dinor-TxB_2 enables us to study the dynamics of the in vivo synthesis of thromboxane A_2 in a continuous fashion.

In the present study, unaltered levels of this urinary metabolite during the first 6 hours of ECMO do not exclude an initial (first-passage) activation of platelets with thromboxane A_2 release. Platelet activation and its subsequent release of thromboxane A_2 have been shown to lead to the activation of the coagulation system [18]. Because the coagulation system showed no significant activation and the total platelet count remained unaltered in this study, a significant activation of platelets is unlikely.

In summary, these clinical and laboratory investigations suggest that 24-hour heparin-free veno–right ventricular ECMO with an endpoint attached and covalently bonded heparin-coated ECMO system does not disturb the coagulation cascade or the blood platelet function significantly in healthy juvenile pigs. In addition, for the evaluation of coagulation factors during major extracorporeal circulation, blood and plasma volume changes ought to be taken into consideration.

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Notice From The Society of Thoracic Surgeons

New Poster Session at STS Annual Meeting

The Program Committee of The Society of Thoracic Surgeons has added a Poster Session to the Twenty-ninth Annual Meeting, which will be held at the San Antonio Convention Center in San Antonio, Texas, January 25–27, 1993. Abstracts may be submitted for the Scientific Session, the Poster Session, or either session using the regular abstract form published elsewhere in this issue and also available from the STS headquarters, 401 N Michigan Avenue, Chicago, IL 60611 (telephone: (312) 644-6610).

Be sure to identify in the designated area the session for which the abstract is being submitted. Presenters will be responsible for developing their poster displays. Details on poster specifications will be furnished after acceptance.

Multivariate Analysis of Postoperative Complications After Esophageal Resection

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To determine the contributing factors for eight postoperative complications after esophagectomy through a right thoracoabdominal approach, a multivariate analysis was carried out on preoperative and intraoperative variables in 141 patients with thoracic esophageal cancer. Although postoperative complications occurred in 125 patients, only 7 died of such complications. The multivariate analysis indicated that the retrosternal route was a significant factor predisposing to postoperative atelectasis. Age, preoperative arterial oxygen tension, and volume transfused were significant factors predisposing to postoperative hypoxemia, whereas age, routes other than the intrathoracic route, and volume transfused were significant factors predisposing to prolonged respiratory support. In addition, preoperative total serum bilirubin level and volume transfused were significant factors predisposing to postoperative hyperbilirubinemia; preoperative serum creatinine level was a significant contributing factor for postoperative renal insufficiency; and sex, antesternal route, and substituted colon were significant contributing factors for anastomotic leakage. There were no significant factors predisposing to postoperative pneumonia and liver dysfunction. These significant factors should be taken into consideration not only during perioperative management but also when choosing the operative procedures and extending the surgical indication for esophagectomy through a right thoracoabdominal approach.

(Ann Thorac Surg 1992;53:1052–6)

Despite advances in operative procedures and perioperative management, the general prognosis for esophageal cancer remains unsatisfactory. Our previous study [1], based on a multivariate analysis, showed the DNA content of cancer cells, resectability of the malignant lesion, and postoperative complications all to be significant prognostic factors in esophageal cancer. Of these three prognostic indicators, only the DNA content appears to be independent of medical intervention. Regarding resectability, we usually perform esophagectomy and radical lymph node dissection through a right thoracoabdominal approach, as it is usually not adequate just to dissect lymph nodes in the upper mediastinum through a left thoracotomy or a transhiatal approach [2–4].

The occurrence of postoperative complications is related not only to perioperative management but also to preoperative assessment variables, clinicopathological findings, and operative variables. Because these factors are often interrelated, a simultaneous multifactorial analysis helps make a fairly accurate evaluation of contributing factors. There has been, however, very little documentation of data for a multivariate analysis of postoperative complications after esophageal resection and reconstruction. This study was done using a multivariate analysis to identify any independently significant factors that might contribute to postoperative complications after esophageal resection and reconstruction through a right thoracoabdominal approach.

Material and Methods

One hundred eighty-six patients with esophageal cancer underwent esophagectomy at the Second Department of Surgery, Kyushu University Hospital, from 1984 to 1989. For this study, 141 patients with squamous cell carcinoma of the thoracic esophagus were selected. All underwent esophagectomy with a right thoracoabdominal approach and reconstruction in one stage using stomach in 135 patients and colon in 6. The operations were preceded by preoperative treatment consisting of hyperthermia, chemotherapy, and radiotherapy [5] in 51 patients or chemotherapy and radiotherapy in 71 patients; 19 patients received no preoperative treatment. The results of the preoperative assessment of and the clinical and histopathological findings in these 141 patients are shown in Tables 1 and 2, respectively.

Esophagectomy and lymph node dissection were done using a right thoracoabdominal approach, with reconstruction through the antesternal, retrosternal, or intrathoracic (posterior mediastinal) route (Table 3). At our hospital, the intrathoracic route is not normally used for reconstruction because of the possibility of local recurrence in the posterior mediastinum [2, 3]. The cervical approach was used for anastomosis through the antesternal or retrosternal route [2, 3]. All patients were supported by mechanical ventilation after operation [6]. Res-

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piratory support was provided for as short a time as possible, and the decision to extubate was based on cough dynamics [6] and oxygenation ratio [7].

In this study, postoperative complications were defined as follows:

1. Pneumonia: infiltrate on chest roentgenogram, positive bacteriological sputum culture, or both
2. Atelectasis: collapse on chest roentgenogram and requirement of a bronchoscopic toilet
3. Hypoxemia: oxygenation ratio (alveolar oxygen tension/arterial oxygen tension) greater than 2.0 during the period of respiratory support
4. Prolonged respiratory support: more than 4 days of postoperative respiratory support
5. Liver dysfunction: level of serum glutamic-pyruvic transaminase greater than 100 IU/L
6. Hyperbilirubinemia: level of total serum bilirubin more than 42.75 μmol/L (2.5 mg/dL)
7. Renal insufficiency: serum creatinine level greater than 106.08 μmol/L (1.2 mg/dL)
8. Anastomotic leakage: radiological evidence of dehiscence of the anastomosis requiring surgical repair.

All data regarding the preoperative variables, ie, preoperative assessment and past history (see Table 1) and clinical and histological findings (see Table 2), and the operative variables (see Table 3) were stored in an IBM 4381 mainframe computer. The Biomedical Computer Program (BMDP) was used for all statistical analyses. The BMDP PLR program was used to determine which variables were independently significant contributing factors for each postoperative complication, using a stepwise logistic regression analysis [8, 9].

Results

Postoperative complications occurred in 125 patients (Table 4). Twelve of the 141 patients died postoperatively in the hospital. Four died of cancer and 1, of renal failure resulting from the contrast medium. Seven patients (5.6% of those with postoperative complications) died of a postoperative complication: 4, pulmonary complications, and 3, mediastinitis resulting from anastomotic leakage.

The multivariate analysis determined 10 independently significant contributing factors for six postoperative complications (Table 5). There were no significant contributing factors for pneumonia and liver dysfunction. The variables for history, histopathological findings, and preoperative treatment were not significant factors predisposing to any postoperative complications.

Age in the clinical findings was a contributing factor predisposing to hypoxemia and prolonged respiratory support. Arterial oxygen tension in the preoperative assessment was determined to be a contributing factor for hypoxemia, but no spirometric variables were significant factors. The retrosternal route and routes other than the intrathoracic route were contributing factors predisposing to atelectasis and prolonged respiratory support, respectively. The volume transfused was a contributing factor for both hypoxemia and prolonged respiratory support. The duration of operation or of anesthesia, the volume of blood lost, and the stage of the tumor were not significant factors predisposing to pulmonary complications.

Table 1. Preoperative Assessment and History of 141 Patients With Thoracic Esophageal Cancer[a]

Assessment and History	Abnormal Range	No. of Patients
Blood analysis		
Serum protein	<6.0 g/dL	13 (9.2)
Serum albumin	<3.5 g/dL	33 (23.4)
Red blood cell count	<400/μL	75 (53.2)
Hemoglobin	<12 g/dL	48 (34.0)
Pulmonary function		
%FVC	<80%	30 (21.3)
$\%FEV_1$	<75%	34 (24.1)
PaO_2	<80 mm Hg	26 (18.4)
Cardiac function		
ECG[b]		35 (24.8)
Master's two-step test	Positive	13 (9.2)
Hepatic function		
SGOT	>40 IU/L	11 (7.8)
SGPT	>40 IU/L	22 (15.6)
LDH	>480 IU/L	2 (1.5)
Indocyanine green test	>10%	48 (34.1)
Total serum bilirubin	>1.2 mg/dL	2 (1.5)
Renal function		
Serum creatinine	>1.2 mg/dL	8 (5.7)
BUN	>20 mg/dL	8 (5.7)
Creatinine clearance	<50 mL/min	11 (7.8)
History		
Diabetes mellitus	. . .	12 (8.5)
Angina pectoris	. . .	7 (5.0)
Pulmonary tuberculosis	. . .	15 (10.6)
Liver dysfunction	. . .	15 (10.6)

[a] Numbers in parentheses are percentages. [b] Abnormal findings included atrial fibrillation, ventricular premature beats, left ventricular hypertrophy, and complete left bundle-branch block.

BUN = blood urea nitrogen; ECG = electrocardiogram; LDH = lactate dehydrogenase; PaO_2 = arterial oxygen tension; $\%FEV_1$ = percentage of forced expiratory volume in 1 second; %FVC = percentage of forced vital capacity; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase.

Preoperative total serum bilirubin and serum creatinine levels, which were within the normal ranges in most patients (see Table 1), were determined to be significant factors for hyperbilirubinemia and renal insufficiency, respectively, but serum albumin level, transaminase level, and creatinine clearance were not significant factors. The volume transfused was a contributing factor for hyperbilirubinemia but not for liver dysfunction. The antesternal route, the use of colon as a substitute, and sex were significant factors predisposing to anastomotic leakage.

Table 2. Clinical and Histopathological Findings in 141 Patients With Thoracic Esophageal Cancer[a]

Variable	No. of patients[b]
Age (y)	62.8 ± 9.6[c]
Sex	
Male	122 (86.5)
Female	19 (13.5)
Location of cancer	
Upper	22 (15.6)
Middle	95 (67.4)
Lower	24 (17.0)
Length of cancer (cm)	5.8 ± 2.4[c]
Depth of penetration	
No invasion to adventitia	20 (14.2)
Invasion to adventitia	84 (59.6)
Invasion into neighboring structure	37 (26.2)
Lymph node metastasis	
Negative	75 (53.2)
Positive	66 (46.8)
Stage	
0	1 (0.7)
I	26 (18.4)
IIa	36 (25.5)
IIb	9 (6.4)
III	44 (31.2)
IV	25 (17.7)
Preoperative treatment	
None	19 (13.5)
Chemotherapy + radiotherapy	71 (50.4)
Hyperthermia + chemotherapy + radiotherapy	51 (36.2)

[a] Numbers in parentheses are percentages. [b] The number of patients is provided unless otherwise indicated. [c] Mean ± standard deviation.

Table 3. Intraoperative Variables in 141 Patients Operated on Through Right Thoracoabdominal Approach[a]

Variable	No. of Patients[b]
Operation time (min)	247 ± 71[c]
Anesthesia time (min)	394 ± 81[c]
Anesthetic	
Halothane	11 (7.8)
Enflurane	130 (92.2)
Blood lost (g)	555 ± 385[c]
Transfusion	
Yes	77 (54.6)
No	64 (45.4)
Volume (mL)	471 ± 715[c]
Substitute in reconstruction	
Stomach	135 (95.7)
Colon	6 (4.3)
Route for reconstruction	
Antesternal	72 (51.1)
Retrosternal	36 (25.5)
Intrathoracic	33 (23.4)
Lymph node dissection	
Yes	97 (68.8)
No	44 (31.2)

[a] Numbers in parentheses are percentages. [b] The number of patients is provided unless otherwise indicated. [c] Mean ± standard deviation.

Comment

Although we avoided operating on patients with seriously impaired pulmonary, cardiac, renal, or hepatic function and used either a two-stage operation [10] or a transhiatal resection without thoracotomy for patients with pulmonary dysfunction, we most often performed esophagectomy and radical lymph node dissection through a right thoracoabdominal approach in consideration of the resectability of malignant lesions [2–4]. Recently, both the morbidity and the mortality after surgical intervention for esophageal cancer have decreased, and most postoperative complications do not usually lead directly to death [1, 4, 11]. Postoperative complications, however, often delay or cause the cancellation of postoperative treatment such as radiotherapy or chemotherapy.

Although the incidence of postoperative pneumonia and atelectasis was 38.8% from 1972 to 1982 at our hospital [12], the incidence was remarkably reduced in this series. Pulmonary complications, however, are still important problems because of both the increase in the indications for surgical operation and the extension of lymph node dissection [13]. According to Tisi [14], there are three possible mechanisms of atelectasis: (1) retained secretions; (2) absence of or decreased sighing, and (3) decrease in expiratory reserve volume. Postoperative mechanical ventilation is indicated for frequent suction to remove retained secretions and makes possible an adequate tidal volume [6]. Substitution through the retrosternal route is suggested to be the cause of the decrease in expiratory reserve volume, as the esophageal substitute occupies a part of the thoracic cavity.

In general, the main causes of postoperative hypoxemia

Table 4. Postoperative Complications in 141 Patients Operated on Through Right Thoracoabdominal Approach[a]

Complication	No. of Patients
Pneumonia	12 (8.5)
Atelectasis	12 (8.5)
Hypoxemia	56 (39.7)
Prolonged respiratory support	43 (30.5)
Liver dysfunction	74 (52.5)
Hyperbilirubinemia	27 (19.1)
Renal insufficiency	20 (14.2)
Anastomotic leakage	19 (13.5)

[a] Numbers in parentheses are percentages.

Table 5. Results of Multivariate Analysis of Preoperative and Operative Variables in Relation to Postoperative Complications

Postoperative Complication	Contributing Factor	p Value	Regression Coefficient
Pneumonia	None	. . .	. . .
Atelectasis	Retrosternal route	0.003	0.949
Hypoxemia	Age	0.007	0.458
	Preoperative PaO_2	0.023	−0.476[a]
	Volume transfused	0.047	0.646
Prolonged respiratory support	Age	0.050	0.442
	Intrathoracic route	0.002	−0.862[a]
	Volume transfused	0.046	0.576
Liver dysfunction	None	. . .	. . .
Hyperbilirubinemia	Preoperative total serum bilirubin	0.037	1.857
	Volume transfused	<0.001	0.158
Renal insufficiency	Preoperative serum creatinine	<0.001	7.300
Anastomotic leakage	Female sex	0.002	−8.680[a]
	Antesternal route	0.032	0.682
	Substituted colon	<0.001	1.916

[a] A negative regression coefficient means that there was a lower incidence of this complication among patients with the determined variable than among those without the variable, or among patients with a higher value for the variable than among those with a lower value.

PaO_2 = arterial oxygen tension.

are an imbalance in the distribution of ventilated blood and increased shunting resulting from diffuse atelectasis [15]. In this study, age was a significant contributing factor for both hypoxemia and prolonged respiratory support, and preoperative arterial oxygen tension was a significant factor predisposing to hypoxemia. Similar findings have previously been reported by Fan and coworkers [16]. They demonstrated that patient age, preoperative serum albumin level, preoperative arterial oxygen tension, and number of surgical wounds were risk factors contributing to postoperative pulmonary complications. Age has also been shown to increase the risk of postoperative morbidity and mortality [12, 14, 16]. This is related to the normal physiological effects of aging and the loss of protective airway reflexes with aging, which decreases the ability to clear secretions [14]. Although there is no relationship between the preoperative spirometric variables and postoperative pulmonary complications [12, 16], preoperative arterial oxygen tension has been shown to be an important predictor of postoperative hypoxemia in this multivariate analysis. The volume transfused was determined to be a significant factor predisposing to hypoxemia and prolonged respiratory support, even though blood transfusions were needed for the maintenance of an adequate circulatory state. The volume transfused may also be representative of the severity of operative damage in each patient.

Cervical procedures are performed through the antesternal or retrosternal route, both of which were determined to be significant contributing factors for prolonged respiratory support. Cervical wound pain can induce stiffness in the neck, which impedes coughing and respiratory movement. The replacement of the cervical esophagus creates a defect in the supporting tissue posterior to the trachea, and this induces instability in the cough movement of the trachea. Our previous study [6] demonstrated a lower cough ability in patients who underwent cervical procedures than in those who underwent intrathoracic reconstruction. Further, injury to the recurrent nerve during cervical procedures seems to influence postoperative pulmonary function, and recurrent nerve paralysis was diagnosed clinically and endoscopically in one third of the patients who underwent cervical procedures.

Although various factors, such as resorption of hematoma or impaired hepatocelluar function resulting from hypotension, hypoxemia, or drugs, might contribute to the development of hyperbilirubinemia [17], a pigment overload because of transfusion was considered to be the main cause of postoperative hyperbilirubinemia, as most hyperbilirubinemia in this study occurred in the early postoperative period.

Preoperative total serum bilirubin and serum creatinine levels were determined to be significant factors, even though in the preoperative assessment, their values were outside the normal ranges in only a few patients. This indicates that high values within the normal limits for total serum bilirubin and serum creatinine can be helpful in predicting the occurrence of postoperative hyperbilirubinemia and renal insufficiency, respectively.

At our hospital, the stomach is the organ most frequently used for substitution because it provides both adequate length and an excellent blood supply [2]. Colon interposition is performed only when a previous gastric operation precludes use of the stomach. Although the main advantage of antesternal reconstruction is that fatal intrathoracic complications can be avoided, one disadvantage of this route is the possibility of ischemia developing in the distal portion of the substitute, as it is longer than other routes. Sex was determined to be a significant factor for anastomotic leakage because no anastomotic leakage occurred in the 19 female patients in this study. The cause of the difference between the sexes remains unclear; future study will be necessary.

In summary, a multivariate analysis determined 10 independently significant contributing factors for six postoperative complications. These significant factors among the preoperative and operative variables should be taken into consideration to better prevent postoperative complications not only when determining the perioperative management but also when choosing the operative procedures and extending the surgical indication for esophagectomy with a right thoracoabdominal approach.

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Retrogastric Versus Antegastric Routing and Histology of the Right Gastroepiploic Artery

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To maximize use of the right gastroepiploic artery in myocardial revascularization 11 cadavers were studied to determine the shortest route (retrogastric versus antegastric) of the right gastroepiploic artery from its origin to the recipient coronary artery. Any coronary artery could be reached with an in situ right gastroepiploic artery. There was no significant difference between the retrogastric and antegastric routes for any coronary artery, although the former generally is slightly shorter to the vessels on the posterior surface of the heart and the latter to vessels on the anterior surface of the heart. Histological examination of the right gastroepiploic artery in its proximal, mid, and distal segments showed a similar width of intima and media and invariably an almost purely muscular media. Based on the histological similarity of the right gastroepiploic artery to the coronary artery, some scepticism toward liberal use of the right gastroepiploic artery, especially if used as a free graft, is warranted until clinical studies on its long-term patency have been performed.

(Ann Thorac Surg 1992;53:1057–61)

The increase in the complexity and quantity of myocardial revascularization procedures, frequently in patients who lack suitable bypass conduits, and the potential advantage of arterial conduits in comparison with venous conduits with regard to long-term patency have promoted the use of alternative arterial conduits such as the right gastroepiploic artery (GEA) and the inferior epigastric artery in addition to the widely used internal mammary artery (IMA) [1–11]. After a recent study by Vander Salm and colleagues [12], in which the shortest route for both IMAs to feasible recipient coronary arteries was established, a comparable study for the GEA, incorporating both retrogastric and antegastric routing, is warranted to optimize use of this arterial conduit in myocardial revascularization. In addition, we studied the histology of the GEA in its proximal, mid, and distal segments with emphasis on the width of the intima and media and the histological condition of the media.

Material and Methods

Eleven autopsies were performed through a Rokitansky incision on 7 women and 4 men who had died of noncardiac diseases. The average age was 67.9 ± 7.5 years (± standard deviation), the average weight was 69.1 ± 10.6 kg, and the average height was 168.1 ± 9.7 cm.

The pericardium and the peritoneum were opened in the midline. The GEA was identified on the greater curvature of the stomach and dissected, with a 3-cm-wide pedicle, in the distal direction to where its luminal diameter became less than 1 mm in diameter, estimated with calibrated probes. Segments 1 cm in length were cut off at the distal GEA until an internal diameter of 1.5 mm was measured. Proximally the GEA was isolated just distal to its origin from the gastroduodenal artery. Subsequently, a transverse slit with a length of approximately 8 cm was created in the diaphragm, which was exposed by dividing the left triangular ligament of the liver, so that there was no or only very little angulation in the GEA at the diaphragm during the various measurements.

In all patients the retrogastric route of the GEA conduit was posterior to the left lobe of the liver and medial to the caudate lobe of the liver, through the omental bursa and the divided lesser omentum (Fig 1). In 8 patients the antegastric route was anterior to the left lobe of the liver (Fig 2), whereas in the remaining 3, who all had hepatomegaly, the GEA conduit was routed posterior to the left lobe of the liver (Fig 3). The right coronary artery, the posterior descending artery, the circumflex and diagonal branches of the left coronary artery, and the left anterior descending artery were marked in their mid segments and always at the same point, to which the underlying coronary artery would most commonly be grafted. All measurements were taken from a string draped with minimal slack from the origin of the GEA to the various marked coronary arteries. To minimize the variables in measuring technique the same individual (G.T.) made all measurements.

After the measurements the GEA was taken out and fixed in flaccid state in 4% formaldehyde solution. Multiple transverse sections with a thickness of 6 μm were obtained at the origin of the GEA conduit, at its mid

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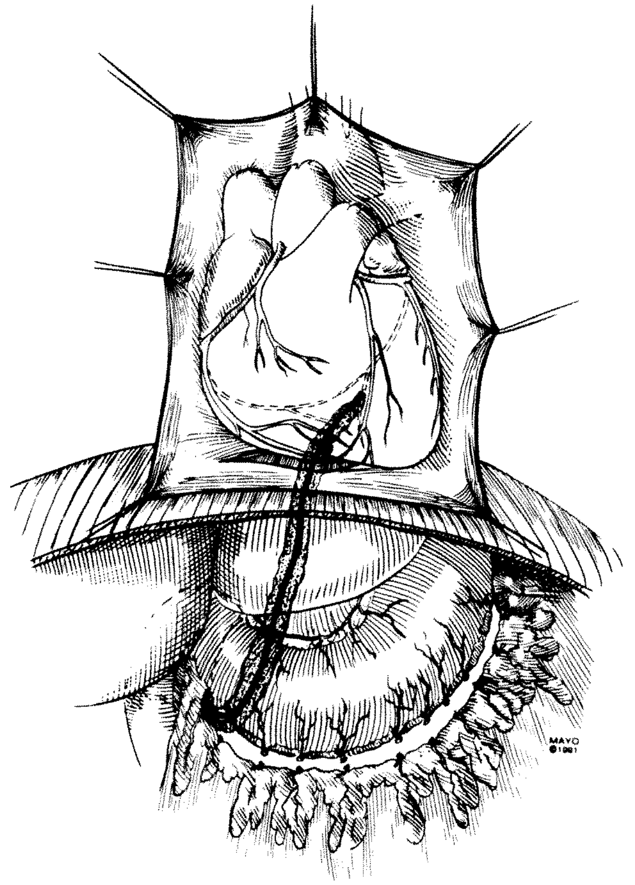

Fig 1. Retrogastric routing of the right gastroepiploic artery, behind the left lobe of the liver and through the omental bursa and the lesser omentum, to the distal right coronary artery and the circumflex branch of the left coronary artery. In a similar fashion the right gastroepiploic artery can be routed toward the main right coronary artery, the left anterior descending artery, and the diagonal branch of the left coronary artery.

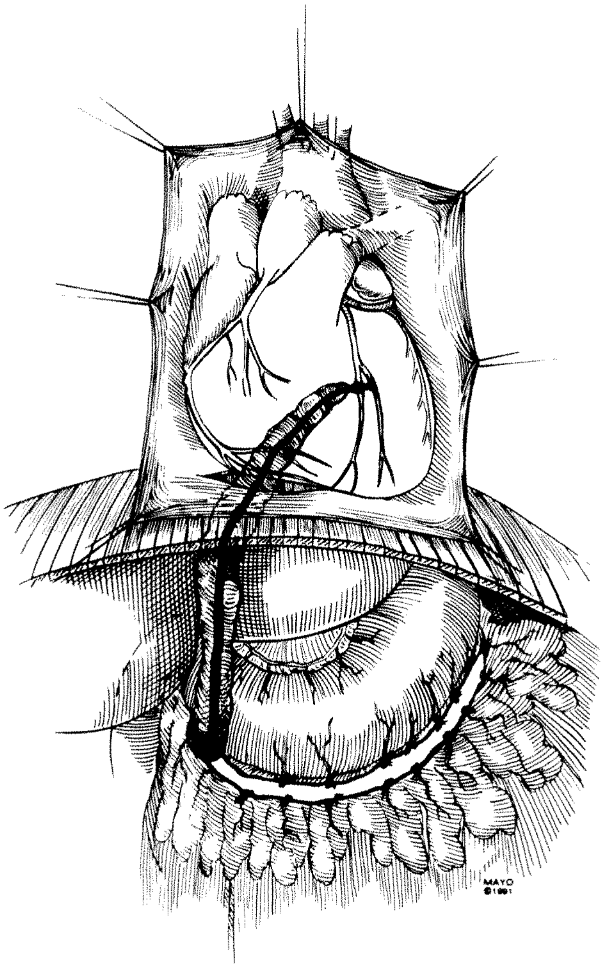

Fig 2. Antegastric routing of the right gastroepiploic artery, anterior to the left lobe of the liver, to the left anterior descending artery and the diagonal branch of the left coronary artery. In a similar fashion the right gastroepiploic artery can be routed toward the main and distal right coronary artery and the circumflex branch of the left coronary artery.

segment, and at its end, and stained by hematoxylin-eosin and elastin-trichrome after Masson. Subsequently, the width of the intima and media was measured at four random locations per section and the histological condition of the media was studied.

Student's paired *t* test and the Wilcoxon signed-rank test (95% confidence limit) were used to assess differences between the retrogastric and antegastric routing. Student's *t* test was used to assess differences in width of intima and media of the GEA among its proximal, mid, and distal segments. A *p* value of 0.05 or less was considered to indicate statistical significance.

Results

In all patients all coronary arteries could be reached with the GEA. The length of the harvested GEA conduits varied from 25 to 31 cm (mean, 26.7 ± 1.9 cm). The distances from the GEA origin to the coronary arteries, using the retrogastric and antegastric routes, are shown in Table 1. In none of the patients was there a significant difference between the two routes. The retrogastric route was slightly shorter to the right coronary artery, posterior descending artery, and circumflex branch of the left coronary artery, whereas the antegastric route was slightly shorter to the diagonal branch and the left anterior descending artery.

In all patients, irrespective of the harvesting site, the media of the GEA consisted primarily of smooth muscle cells, with rare elastic fibers dispersed in between, and was limited by the internal and external elastic laminae (Fig 4). The width of intima and media in the proximal, mid, and distal segments of the GEA is listed in Table 2. There was no significant difference in the width of intima and media among the three segments. In the proximal versus the mid and distal segments the intima was slightly thicker, but this did not reach statistical significance.

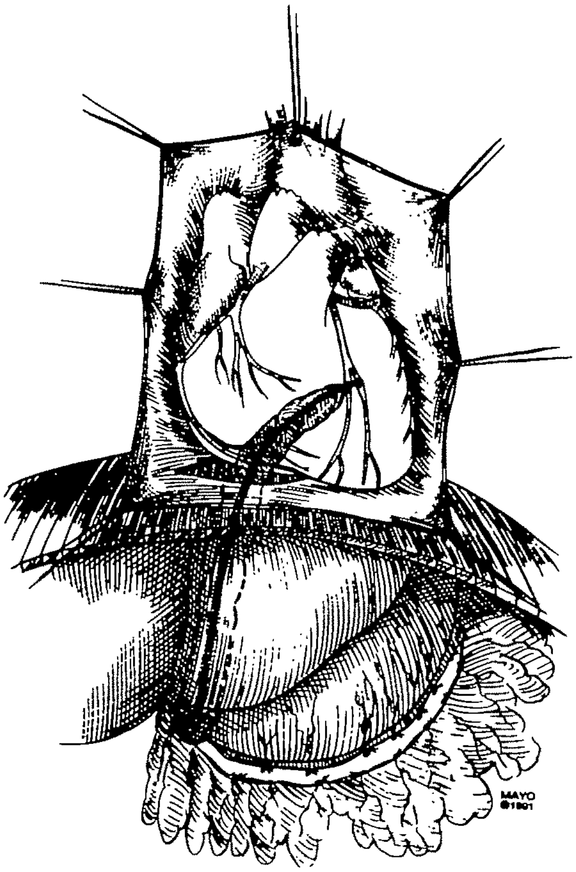

Fig 3. Antegastric routing of the right gastroepiploic artery, posterior to the left lobe of the liver, to the left anterior descending artery and the diagonal branch of the left coronary artery. This route may be shorter in patients with hepatomegaly. In a similar fashion the right gastroepiploic artery can be routed toward the main and distal right coronary artery and the circumflex branch of the left coronary artery.

Comment

In this study all coronary arteries could be reached with the GEA. The shortest route to the main right coronary artery, the posterior descending artery, and the circumflex branch was retrogastric and posterior to the left lobe of the liver. The shortest route to the diagonal branch and the left anterior descending artery was antegastric, usually anterior to the left lobe of the liver (although in some cases of hepatomegaly a route posterior to the left lobe of the liver was shorter). There was no statistically significant difference in length between the retrogastric and antegastric routes. Our data confirm the clinical findings of Mills and Everson [5] and Lytle and co-workers [8] that retrogastric (versus antegastric) routing may be more appropriate for the posterolateral branches of the right coronary artery and the circumflex artery. Contrary to the recommendation by Lytle and associates [8], however, we believe that the retrogastric route is also appropriate for the main right coronary artery. The diagonal branch and the left anterior descending artery are generally better reached antegastrically. In both routings the GEA, when appropriately mobilized, crosses the pylorus (or the distal antrum) and not the stomach. Therefore, potential problems arising from tension on the pedicle with gastric dilation are unlikely. An advantage of retrogastric routing versus antegastric routing consists of a lesser risk of injury during later laparotomy [7]. A disadvantage of retrogastric routing may be the more difficult control of bleeding, but we believe that ligation of the GEA branches instead of stapling is an adequate safeguard against this complication [8, 13].

Table 1. Retrogastric and Antegastric Distance From the Origin of the Right Gastroepiploic Artery to the Various Coronary Arteries

Artery	Distance (cm)[a] Retrogastric	Distance (cm)[a] Antegastric	p Value[b]	95% Confidence Interval[c]
RCA	19.3 ± 1.1	20.7 ± 1.2	NS	−1.72, 0.46
PDA	20.4 ± 1.6	21.8 ± 1.4	NS	−1.39, 0.39
Cx	23.8 ± 1.0	24.3 ± 1.5	NS	−1.27, 0.27
LAD	24.5 ± 1.3	23.1 ± 1.8	NS	−0.82, 1.07
Dg	26.1 ± 1.6	24.7 ± 1.7	NS	−0.63, 1.12

[a] Data are shown as the mean ± standard deviation. [b] Student's paired *t* test. [c] Wilcoxon signed-rank test.

Cx = circumflex branch of left coronary artery; Dg = diagonal branch of left coronary artery; LAD = left anterior descending coronary artery; NS = not significant; PDA = posterior descending coronary artery; RCA = right coronary artery.

In the performance of this study some caveats must be raised. First, the measurements may seem somewhat subjective, because the degree of gastric filling was not similar between the various patients. However, as stated before, the degree of gastric filling hardly influenced the measured length of the GEA conduit because the GEA crossed the pylorus (and in a minority of the patients the distal antrum) rather than the stomach. Second, the conditions in a cadaver are different from those in a living patient with regard to filling and compressibility of the heart and motion of the lungs. Furthermore, in the living patient it may not always be easy to isolate the GEA to its origin from the gastroduodenal artery owing to abundant presence of fat and potential bleeding from small vessels in that area. Therefore, the harvesting technique of the GEA as described in this study may slightly overestimate the available length of the GEA.

Vander Salm and co-workers [12] have shown that all coronary arteries can be reached with one or both in situ IMA grafts. Because not all of the coronary arteries can be revascularized with IMA grafts, we recommend that the IMAs should be used primarily to graft the left-sided coronary arterial circulation, whereas the right coronary artery can be grafted with the GEA or with a venous conduit [14]. If for various reasons suitable IMAs are not available, the GEA may be used to revascularize the left-sided vessels. Use of in situ arterial grafts has the additional advantage of avoidance of a proximal anastomosis, which may be a considerable advantage in the severely calcified ascending aorta [15].

Contrary to the statements of Mills and Everson [5] that intimal hyperplasia and atherosclerosis of GEA grafts are

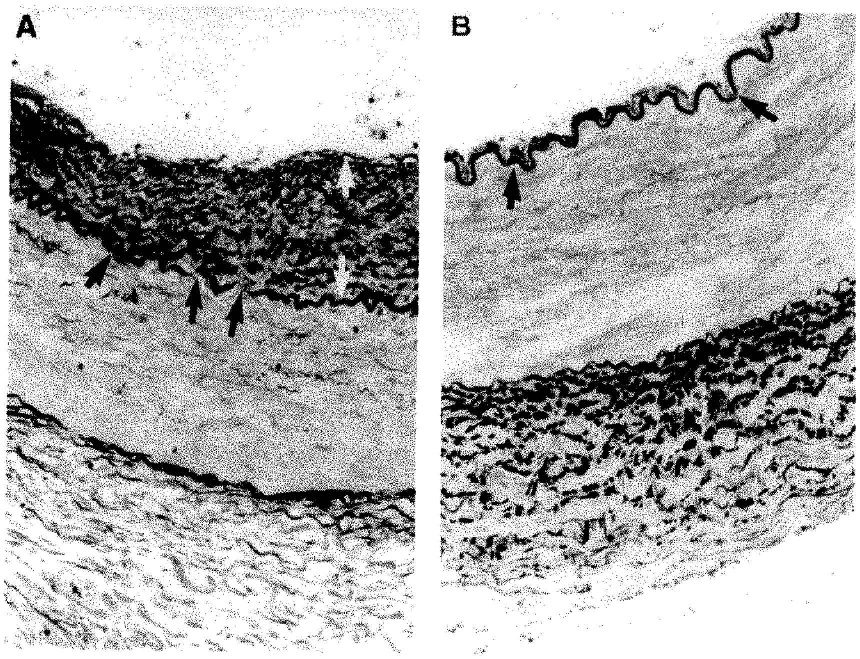

Fig 4. Example of histology of the right gastroepiploic artery. (A) At its origin from the gastroduodenal artery. (B) At the distal end of the harvested conduit. Note the purely muscular content of the media, the discontinuities in the internal elastic lamina (black arrows)*, and the moderate to rather severe intimal thickening* (white arrows) *in the proximal segment. (Elastine-trichrome after Masson stain; original magnification ×140.)*

unlikely and of Suma and associates [16] that excellent long-term patency similar to IMA grafting can be expected with the GEA, we believe that some scepticism toward the long-term patency of the GEA conduit is warranted, especially if the GEA is used as a free graft. We base this scepticism on our thorough histological studies of the coronary arteries and various arterial conduits in myocardial revascularization, in which the GEA resembles the coronary artery with regard to the almost purely muscular content and thickness of its media [17, 18]. In recent studies we documented a significantly greater number of discontinuities in the internal elastic lamina in the muscular segments versus the elastic and elastomuscular segments of the IMA [19, 20]. Similarly, the number of discontinuities in the internal elastic lamina in the muscular GEA is greater than that in the elastic segments of the IMA [18]. This observation most likely reflects the protective effect of elastic lamellae in the media against the development of discontinuities in the internal elastic lamina, and, secondarily, against migration and proliferation of smooth muscle cells from the media into the intima [21–23]. The histological similarity between the GEA and coronary artery may find expression in an increased vulnerability toward intimal thickening and, ultimately, atherosclerosis of the GEA once its wall is exposed to the forceful mechanical stretching of the central aortic circulation (if used as a free graft) and (to a lesser extent) the coronary circulation. Thus, although Suma and associates [16, 24] and we found only a mild to moderate degree of intimal thickening in the GEA (with slightly more intimal thickening at the origin of the GEA in our study), this finding must be interpreted with caution, because it reflects the situation at the time of harvesting of the GEA in its natural environment. Future clinical studies with regard to the long-term patency rate of the GEA in myocardial revascularization will prove whether our scepticism is justified or not.

Table 2. Width of Intima and Media of the Right Gastroepiploic Artery at its Proximal, Mid, and Distal Segments

Layer	Width (μm)[a] Proximal	Mid	Distal	p Value[b]
Intima	58.9 ± 41	37.3 ± 22	40.8 ± 33	NS
Media	245.9 ± 107	253.7 ± 103	187.1 ± 38	NS

[a] Data are shown as the mean ± standard deviation. [b] Student's t test.
NS = not significant.

The conclusions reached from this study are as follows: (1) In most situations, after adequate mobilization and with proper routing, any coronary artery can be reached with the GEA conduit. (2) Retrogastric routing of the GEA conduit was not significantly different from antegastric routing in terms of required length of the conduit to the various coronary arteries, although the retrogastric route generally is slightly shorter to the posterior surface of the heart and the antegastric route generally is slightly shorter to the anterior surface of the heart. (3) Some scepticism toward the long-term patency of the GEA in myocardial revascularization is warranted until clinical studies on this subject have been conducted.

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15

Efficacy of Isoproterenol on the Failing Transplanted Heart During Early Acute Rejection

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Acute rejection often leads to severe myocardial failure and death. The beneficial hemodynamic effects of isoproterenol in improving immediate postoperative heart failure have prompted its routine use after transplantation. However, because of the physiopathological alterations documented during rejection, an inappropriate response of the graft to isoproterenol administration could be expected. Six dogs received orthotopic transplants and were prepared with implantable devices for serial hemodynamic studies. The studies were performed on the resting unanesthetized subject 3 hours after operation when transient heart failure was present and repeated when myocardial failure secondary to rejection occurred. After basal state measurement, various doses of isoproterenol were infused and the hemodynamic responses during each period were compared. During rejection, the hemodynamic response to 0.05 and 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was significantly lower when compared with the response in the postoperative period. To achieve similar postoperative chronotropic and inotropic effects, 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of isoproterenol was necessary. Isoproterenol is therefore effective in controlling myocardial failure during acute rejection despite a reduced sensitivity of the sinoatrial node and myocardial tissue.

(Ann Thorac Surg 1992;53:1062–7)

Heart transplantation is now accepted as a therapeutic alternative for end-stage heart disease in both the adult and pediatric population [1, 2]. Despite its high success rate many problems persist. Early acute rejection of the graft is one of these problems being directly responsible for 18% of the deaths [2]. This physiopathological state often leads to a greatly impaired cardiac function [3, 4]. Inotropic [5, 6] or mechanical [7] support of the graft is therefore necessary to enable subsequent reversal of the rejection phenomenon by intensification of immunosuppression [8] or retransplantation [2, 9].

In cardiac transplantation, myocardial failure is first encountered in the immediate postoperative period resulting from the surgical technique [10]. Because postoperative failure of the graft often occurs among transplant patients, isoproterenol has been routinely used because of its beneficial hemodynamic effects [1, 6, 10].

It has been recognized experimentally [3, 11] for several years that donor heart performance is significantly depressed during advanced stages of acute rejection. During severe unmodified rejection, heart failure was evidenced by a low cardiac output state, reduced systolic and diastolic functions, and high peripheral resistance [4]. Postmortem morphological and histological studies [3, 12–15] revealed structural changes associated with acute rejection. Because of these morphological alterations, one could expect the response of the graft to pharmacological agents to be modified. Hence, various inotropic agents such as calcium [12], digitalis [14, 16], and amrinone [17] were used to attempt correction of graft failure during acute rejection, but all proved unsuccessful. From these findings one could postulate that the use of sympathomimetic amines that induce their positive inotropic and chronotropic effects by stimulating β_1 cardiac receptors would not be beneficial during the physiopathological state of acute rejection. However, we reported in a systematic experimental study that dobutamine was effective in controlling myocardial failure associated with acute rejection despite a reduced sensitivity of the graft. To overcome this reduced sensitivity an increment in dosage was sufficient to improve cardiac index by 118% without detrimental chronotropic effect (unpublished data). Our recent findings prompted us to investigate if isoproterenol, another β-adrenergic agent, was efficient in controlling heart failure during acute rejection.

Material and Methods

Six mongrel dogs weighing an average of 23.4 kg were anesthetized with sodium pentobarbital (25 mg/kg, intravenously). The animals were ventilated by a mechanical respirator with a constant tidal volume of 10 to 12 mL/kg and an inspired oxygen fraction of 0.80 (volume respirator, Harvard model 607). Each animal underwent orthotopic cardiac transplantation according to the modified Shumway technique [3]. During the surgical procedure a polyvinyl catheter was positioned in the descending aorta through the left subclavian artery for blood pressure monitoring. A similar catheter was positioned into the superior vena cava through the left external jugular vein for infusion of isoproterenol. An electromagnetic flow probe (SP 2202; Statham Instruments, Oxford, CA) of appropriate diameter was secured around the ascending

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Table 1. Cardiovascular Effects of Isoproterenol 3 Hours After Operation[a]

Variable	Baseline	Isoproterenol	
		0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Heart rate (beats $\cdot$ min^{-1})	134 ± 16	164 ± 30[b]	190 ± 33[b,c]
Stroke volume index (mL $\cdot$ $beat^{-1}$ $\cdot$ m^2)	8.4 ± 2.6	14.8 ± 5.9[b]	20.3 ± 8.8[b]
Cardiac index (L $\cdot$ min^{-1} $\cdot$ m^2)	1.1 ± 0.5	2.5 ± 1.1[b]	3.7 ± 1.4[b,c]
Stroke work index (J $\cdot$ $(beat \cdot m^2)^{-1}$)	0.11 ± 0.03	0.23 ± 0.08[b]	0.32 ± 0.13[b]
Mean arterial pressure (mm Hg)	92 ± 9	106 ± 8[b]	107 ± 13[b]
Total vascular resistance (mm Hg $\cdot$ L^{-1} $\cdot$ min)	95 ± 37	55 ± 29[b]	35 ± 19[b]

[a] Data are shown as the mean ± standard deviation (n = 6). [b] Significance: $p < 0.05$, compared with baseline values. [c] Significance: $p < 0.05$, comparison between doses.

aorta and allowed accurate recordings of cardiac dynamics. Catheters and flow probe cables were exteriorized dorsally, allowing studies to be performed on the resting unanesthetized dog. Prophylactic antibiotherapy was given daily (Bicillin, 1,200,000 IU) but no immunosuppression was used.

In both hemodynamic studies, each of the following parameters were recorded: electrocardiogram (DII), heart rate (beats $\cdot$ min^{-1}), systolic, diastolic, and mean arterial pressures (mm Hg), cardiac index (L $\cdot$ min^{-1} $\cdot$ m^2), stroke index (L $\cdot$ $beat^{-1}$ $\cdot$ m^2), stroke work index (J $\cdot$ $[beat \cdot m^2]^{-1}$), and total vascular resistance (mm Hg $\cdot$ L^{-1} $\cdot$ min) [4].

Each study was performed when animals were in normal sinus rhythm with no atrial pacing. Maintenance of a normal blood volume was also achieved during the entire postoperative period based on central venous pressure and calculation of blood loss and replacement.

The first study was performed 3 hours after transplantation when cardiac function was depressed [10]. The hemodynamic parameters were first recorded at intrinsic rate, then isoproterenol was infused continuously in successive doses of 0.05 and 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for periods of 5 minutes each while the same parameters were recorded.

Cardiac function, which was monitored daily during the following days, improved progressively until it reached a peak postoperative value 3 to 4 days after operation [4]. The first signs of rejection occurred 5 to 7 days after implantation, as evidenced by a progressive decrement of cardiac function [4].

When, owing to rejection, cardiac function decreased by 40% or more from its peak postoperative value, the second study was carried out. After basal state recording, isoproterenol was infused continuously for 5 minutes at incremental doses of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ from 0.05 to 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$ while the same hemodynamic parameters were recorded. When the terminal phase of rejection was reached and the hemodynamic study was completed, the animal was immediately sacrificed. Macroscopic evidence of rejection was sought, and rejection was confirmed by the presence of severe infiltration, edema, and myocardial necrosis [13], which in all cases was graded as either moderate or severe. All animals were humanely treated in strict accordance with the "Guide for the Care and the Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985). Only those animals in good clinical condition for which a complete and valid hemodynamic study could be carried out during the immediate postoperative period and during acute rejection were retained for data analysis.

The changes in hemodynamic parameters induced by isoproterenol administration, either postoperatively or during acute rejection, were compared with baseline values using the repeated one-way analysis of variance and the Fisher PLSD correction when appropriate. Then the results obtained after infusing each dose of isoproterenol were compared with the previous infusion for both periods using the same statistical tests. Also, the effects of isoproterenol infusions (0.05 and 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during rejection were compared with those of the immediate postoperative period using Student's t test for paired data. Finally, the hemodynamic changes induced with 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of isoproterenol during rejection were compared with those obtained postoperatively after a 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion of the drug using the same t test.

To obtain a stock solution of 20 $\mu g \cdot mL^{-1}$, 2 mg of isoproterenol hydrochloride (Winthrop Laboratories) was diluted in 90 mL of 0.9% sodium chloride injection USP (Travenol Canada Inc) before each experiment. An infusion pump (Travenol Laboratories Inc, Irvine, CA) was used to administer isoproterenol intravenously.

Results

All homotransplanted dogs met the inclusion criterias and served the purposes of this study.

The hemodynamic data gathered 3 hours after implantation of the graft are shown in Table 1. During that period, postoperative myocardial failure was exemplified by low cardiac index, low stroke work, and high peripheral resistance. However, a significant increment of heart rate (22% to 41%), stroke volume (82% to 152%), cardiac index (133% to 255%), stroke work (111% to 211%), and mean arterial pressure (16% to 18%) was observed after isoproterenol administration (0.05, 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), whereas vascular resistance fell (41% to 61%).

Table 2. Cardiovascular Effects of Isoproterenol During Acute Rejection[a]

		Isoproterenol	
Variable	Baseline	0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Heart rate (beats · min^{-1})	141 ± 30	152 ± 30	162 ± 33[b]
Stroke volume index (mL · $beat^{-1}$ · m^2)	11.8 ± 3.4	12.7 ± 3.0	14.4 ± 3.0[b]
Cardiac index (L · min^{-1} · m^2)	1.7 ± 0.6	1.9 ± 0.6	2.4 ± 0.8[b,c]
Stroke work index (J · $(beat \cdot m^2)^{-1}$)	0.14 ± 0.05	0.17 ± 0.04	0.18 ± 0.03[b]
Mean arterial pressure (mm Hg)	75 ± 18	79 ± 16[b]	78 ± 15
Total vascular resistance (mm Hg · L^{-1} · min)	50 ± 18	47 ± 19	38 ± 18[b,c]

[a] Data are shown as the mean ± standard deviation (n = 6). [b] Significance: $p < 0.05$, compared with baseline values. [c] Significance: $p < 0.05$, comparison between doses.

Between doses, only heart rate and cardiac index responses differed significantly.

The cardiovascular effects of isoproterenol obtained during early acute rejection are shown in Table 2. Graft failure secondary to rejection is also evidenced by low cardiac output, reduced stroke work index, and increased vascular resistance. A modest hemodynamic effect was observed after a 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion of isoproterenol as only the increment in mean arterial pressure was significant. However, 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of the drug significantly increased heart rate (15%), stroke index (28%), cardiac output (48%), and stroke work (38%), whereas peripheral resistance fell by 24%. The changes in cardiac index and vascular resistance induced by 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of isoproterenol were significantly different than those induced by 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

During rejection, the response of the graft to 0.05 and 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of isoproterenol was significantly attenuated if compared with the immediate postoperative period (Fig 1). However, comparing the hemodynamic changes obtained with 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of isoproterenol during rejection with those induced postoperatively by 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (Fig 2), we notice that the difference in responses is no longer significant except for blood pressure.

Figure 3 compares the response of the rejecting heart transplant to isoproterenol administration at doses ranging from 0.05 to 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$. With rejection, a dosage increment from 0.05 to 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$ progressively increased the response in heart rate (8% to 34%), stroke volume (10% to 54%), cardiac index (16% to 106%), and stroke work (20% to 59%), whereas a constant decrement in vascular resistance was observed (7% to 51%). No important difference in mean arterial pressure was noted.

Comment

The frequent occurrence of postoperative myocardial failure has been well documented after heart transplantation [10]. Isoproterenol has been used routinely in this situation, and hemodynamic improvement has been frequently observed [6, 10]. The present findings clearly demonstrate the efficacy of isoproterenol in improving myocardial function after transplantation, thus confirming previous observations.

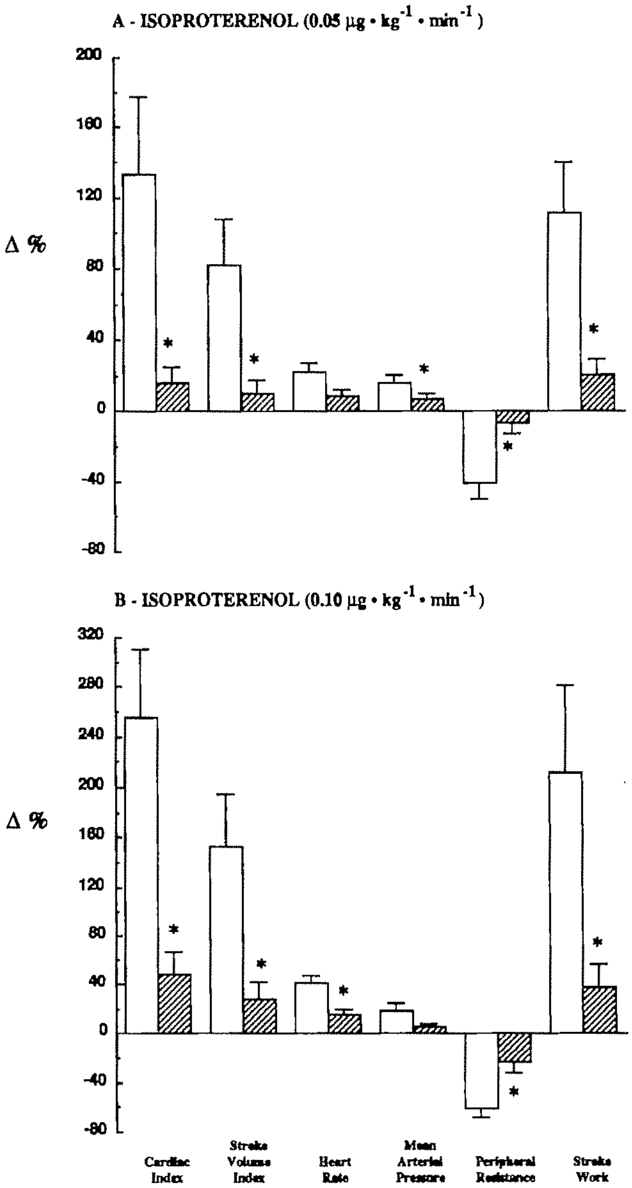

*Fig 1. Comparison of hemodynamic changes (Δ%) induced by (A) 0.05 and (B) 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of isoproterenol during acute rejection versus immediate postoperative period. Data are shown as the mean ± the standard error of the mean (% from baseline). (□ = postoperative period; ▨ = acute rejection period; *$p < 0.05$ rejection versus postoperative period.)*

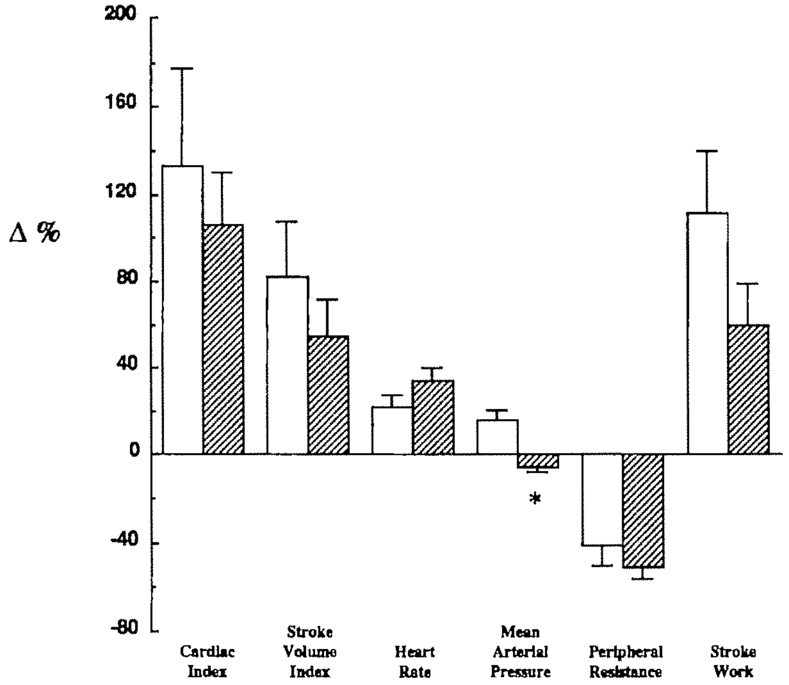

Fig 2. Comparison of hemodynamic changes (Δ%) induced by isoproterenol during acute rejection (0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$) versus immediate postoperative period (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Data are shown as the mean ± the standard error of the mean (% from baseline). (□ = 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$; ▨ = 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$; *$p < 0.05$ *rejection versus postoperative period.)*

Severe heart failure often encountered during acute rejection accounts for 18% of the mortality in heart transplantation [2]. Second to infection, it is the most important cause of death. Thus, it is critical in this situation to control graft failure with pharmacological agents while allowing subsequent reversal of rejection [8] or retransplantation [2, 9]. However, besides 2 case reports [5, 6] and our recent study on dobutamine (unpublished data), no systematic study has evaluated the efficacy of β-adrenergic agents. This prompted us to evaluate isoproterenol during early acute rejection.

Isoproterenol was also chosen for its pharmacological properties. Being a pure β-adrenergic stimulator, it induces an increase in cardiac output resulting primarily from an increment in heart rate [6]. It also has a great inotropic efficacy [18] without inducing vasoconstriction and a rise in arterial blood pressure, which normally occurs with endogenous catecholamines like norepineph-

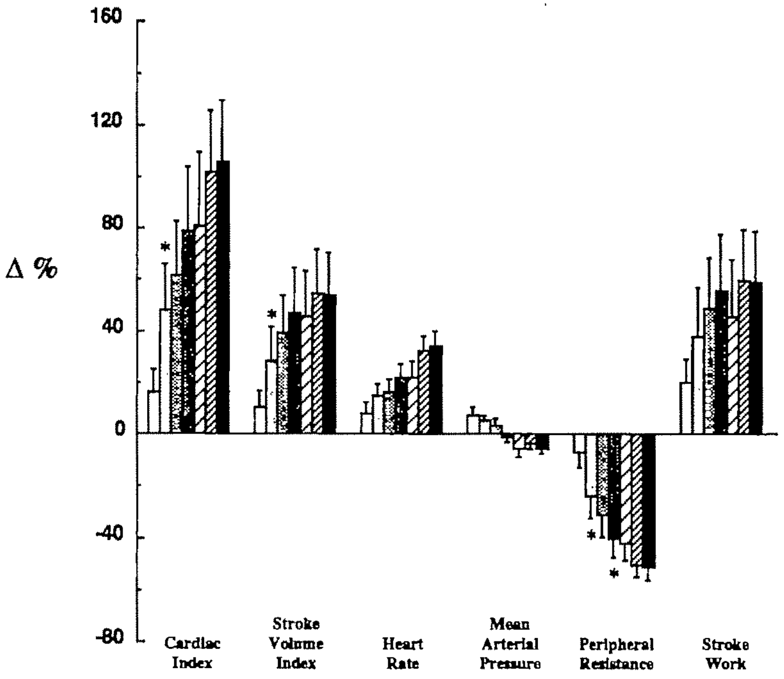

Fig 3. Hemodynamic changes (Δ%) induced by isoproterenol dosage ranging from 0.05 to 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during acute rejection. Data are shown as the mean ± the standard error of the mean (% from baseline). (□ = 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$; ▦ = 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$; ■ = 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$; ▩ = 0.20 $\mu g \cdot kg^{-1} \cdot min^{-1}$; ◪ = 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$; ▨ = 0.30 $\mu g \cdot kg^{-1} \cdot min^{-1}$; ■ = 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$; *$p < 0.05$ *versus adjacent lower dose.)*

rine, epinephrine, and dopamine [19]. Therefore, it appeared to us of clinical importance to determine if its beneficial hemodynamic effects were preserved in early acute rejection and if its undesired chronotropic effects [18, 20] were present and detrimental.

Because of the severe morphological alterations sustained by the graft during acute rejection [3, 12–15], we assumed that isoproterenol would be less effective in controlling myocardial failure during that period. Our data reveal that the failing graft is still sensitive to a 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion of isoproterenol. However, the hemodynamic response is significantly attenuated when compared with the response in the immediate postoperative period. During rejection, a chronotropic effect similar to that obtained 3 hours after transplantation was achieved only after a threefold to fourfold increment in dosage. Hence, a 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion of the drug increased heart rate by 34% compared with the 41% increment induced postoperatively by 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. These results clearly indicate a reduced responsiveness of the homotransplant sinoatrial node to isoproterenol administration during acute rejection, which is consistent with currently evolving concepts of an altered automaticity of the sinoatrial pacemaker tissue during moderate and severe cardiac rejection [21, 22].

Isoproterenol also has a diminished inotropic activity during acute rejection as a result of the pathophysiological alterations sustained by the graft [3, 12–15]. With 0.05 and 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ the increments in both stroke index (10% and 28%) and cardiac index (16% and 48%) are significantly lower in rejection when compared with those of the immediate postoperative period (82% and 152%; 133% and 255%, respectively). However, a sevenfold increase in dosage (0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$) induced an increment in both parameters similar to that attained postoperatively after a 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion of the drug (54% and 106% versus 82% and 133%). These findings also demonstrate a reduced sensitivity of β-adrenergic receptors of the myocardial tissue to isoproterenol. This observation is of clinical importance because higher doses of isoproterenol are necessary during acute rejection to attain near-normal levels of cardiac index. It is interesting to note that with these high doses no deleterious tachycardia or arrhythmia occurred.

Despite a reduced sensitivity of the sinoatrial node and ventricular myocardium to isoproterenol, β-adrenergic stimulation is maintained during rejection. Some mechanisms might be postulated to explain this response. Because the morphological alterations are heterogenous during rejection [13, 15], whereas some parts of the heart are severely damaged, other areas of the sinus node, myocardium, and coronary vasculature are spared to the point of allowing responsiveness of β_1-adrenergic receptors to the drug. Second, despite the known morphological alterations [3, 12–15] and the decrease in β_1 cardiac receptors during heart failure (down-regulation) [23], cardiac denervation may increase the number of these receptors (up-regulation) and their sensitivity to circulating catecholamines [24, 25] to the point that a positive response is maintained.

In conclusion, isoproterenol is effective in improving myocardial failure during the immediate period after transplantation. It is also beneficial during acute rejection with hemodynamic compromise despite a reduced sensitivity of the sinoatrial node and myocardial tissue to isoproterenol. This reduced responsiveness can be overcome by an increment in dosage, allowing near-normal levels of cardiac index with no detrimental chronotropic effect. Whether the efficacy of the drug is maintained after 1 or 2 days is beyond the scope of this experiment.

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Endothelium-Mediated Relaxation in Transplanted Aorta

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This study compares the vasodilating effect of endothelium-derived relaxing factors (EDRFs) in free arterial grafts with that in their normal control vessels. The infrarenal aorta of Sprague-Dawley rats was transplanted into the same position in other inbred recipient rats. A Krebs buffer solution (4°C) served as the preservation solution. The ischemic time for the grafts ($n = 8$) was 42 ± 1 minutes. Two grafts were studied after 3 days and six grafts, after 60 days. Ring segments were cut from all vessels, and isometric contractions were recorded in organ baths. The vessel segments were constricted with noradrenaline, a thromboxane A_2 mimic (U-46619), or prostaglandin $F_{2\alpha}$. Concentration–response curves with acetylcholine, which was used as the endothelium-stimulating substance causing release of EDRFs, were obtained. The patency of the grafts was 100%. Acetylcholine induced relaxation in all vessel segments with intact intima, whereas no relaxation was seen when the endothelium was manually removed. No significant differences were found between the grafts and the normal control vessels. Histology of the 60-day grafts showed elastomuscular arteries without intimal thickening and a media consisting of eight to ten muscle layers interrupted by five to six elastic lamellae. Scanning electron microscopy showed no major differences between normal endothelium and the endothelium of 3-day or 60-day grafts. This study indicates that free elastomuscular arterial grafts, in which the morphology of the intima is preserved, will retain their full ability to release EDRFs.

(Ann Thorac Surg 1992;53:1068–73)

The history of endothelium-derived relaxing factors (EDRFs) started in 1980 when Furchgott and Zawadzki [1] observed that acetylcholine elicited a relaxation of rabbit aortic ring segments only when the preparations were lined with an intact layer of endothelial cells, whereas preparations in which the endothelium had been removed reacted with a contraction. Further research into this field has demonstrated that a number of endogenous substances (eg, acetylcholine, histamine, serotonin, bradykinin, adenosine diphosphate, adenosine triphosphate, and aggregating platelets) can stimulate vascular endothelium to release EDRFs in many species, including humans, both in vitro [2, 3] and in vivo [4, 5]. Increased blood flow rate has also been shown to release EDRFs [6]. Furthermore, EDRFs *per se* have an inhibiting effect on platelet aggregation [7, 8], and this effect is more pronounced when the relaxing factors are released together with prostacyclin [9]. Endothelium-derived relaxing factors have also been shown to inhibit the adhesion of platelets to endothelial cells [10].

Several substances are believed to be endothelium-derived relaxing factors. One of them has been identified as a very simple molecule, namely, nitric oxide. The physiological precursor of nitric oxide is the amino acid L-arginine, which releases nitric oxide in its enzymatic conversion to L-citrulline [11, 12]. Nitric oxide stimulates guanylate cyclase, thereby giving increased levels of cyclic 3′,5′-guanosine monophosphate, which relaxes the vascular smooth muscles [13, 14].

Lüscher and associates [15] suggested that EDRFs, with their vasodilating capacity, antiaggregating effect on platelets, and inhibitory effect on platelet adhesion, may be important for the patency of vascular grafts [15]. However, as van de Voorde [16] pointed out, such a suggestion is valid only if we assume that vascular grafts behave like normal blood vessels. That can be settled only by comparing the reactivity of grafts with the reactivity of their normal control vessels. The aim of the present study was to determine whether endothelium can retain its full ability to release EDRFs in free arterial grafts.

Material and Methods

Sixteen inbred male Sprague-Dawley rats (initial weight, 225 to 275 g) were used for allograft transplantation of the infrarenal aorta: 8 animals served as vessel donors and the others, as recipients. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985). The study was approved by the Ethics Committee of the University of Lund.

Ether was used for anesthesia. The aorta of the donor was clamped below the renal arteries and above the iliac bifurcation and then extirpated between the clamps and immediately put into 4°C Krebs buffer solution with the following composition (in millimoles per liter): NaCl, 119; $NaHCO_3$, 15; KCl, 4.6; $CaCl_2$, 1.5; NaH_2PO_4, 1.2; $MgCl_2$, 1.2; and glucose, 11. All blood was removed from the

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vessel segment by careful injection of the buffer solution. The aorta of the recipient was prepared and clamped in the same way as the donor aorta and divided midway between the clamps. The graft segment was then interposed in its original orientation and sutured end-to-end with resorbable 9-0 Vicryl sutures (Ethicon, Somerville, NJ). Each anastomosis consisted of eight to ten interrupted stitches. The ischemic time for the grafts (n = 8) was 42 ± 1 minutes.

Two months later, the grafts in 6 rats (two grafts were studied after 3 days) were removed between hemostats using the same type of anesthesia. The vessels were immediately placed in warm (37°C) and oxygenated (95% oxygen and 5% carbon dioxide) Krebs buffer solution and cleaned from surrounding connective tissue. Four ring segments (about 1 mm long) were then taken from the midportion of each graft and transferred to temperature-controlled (37°C) organ baths containing 5 mL of Krebs buffer solution, which was bubbled with 95% oxygen and 5% carbon dioxide, giving a pH of approximately 7.4.

Each segment was suspended between two metal holders (0.2 mm in diameter). One of these holders was attached to a Grass FT 03 transducer connected to a Grass polygraph for continuous recording of isometric tension. The other metal holder was fixed to a movable unit by which the vessel segments could be repeatedly stretched until a basal tension of 8 mN was reached (after approximately 1.5 hours). The vessels were then exposed to a potassium-rich (124 mmol/L) buffer solution of the following composition (in millimoles per liter): KCl, 124; $NaHCO_3$, 15; $CaCl_2$, 1.5; NaH_2PO_4, 1.2; $MgCl_2$, 1.2; and glucose, 11. This induced strong contraction in all vessel segments. When the contraction had reached its plateau, the potassium-rich solution was washed away with Krebs solution, allowing the tension to return to its basal value. After half an hour, this procedure was repeated once. This was done to stabilize the vessels before the experiment started.

In another group of 8 fresh rats (normal controls), the infrarenal aorta was extirpated and handled in the same way as the graft vessels. In 50% of the ring segments from each rat, the endothelium was removed by gentle rubbing of the intimal surface over a pair of microtweezers before the segments were mounted in the organ baths. Previous studies [1, 17] have shown that such a technique successfully removes the vascular endothelium without damaging the arterial smooth muscles. The other 50% were studied with an intact endothelium. Some experiments were carried out in the presence of indomethacin, 10^{-7} mol/L, to inhibit the synthesis of vasoactive prostanoids. However, no differences in drug effects were found between segments without and with indomethacin.

Contractions of all vessel segments were induced with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (Amoglandin; Astra, Södertälje, Sweden), U-46619 (a thromboxane A_2 mimic; The Upjohn Company, Kalamazoo, MI), or noradrenalin ((L)-noradrenalin hydrochloride; Sigma, St. Louis, MO) using the lowest possible concentration capable of giving a stable contraction over the time needed to obtain a concentration–response curve with acetylcholine (these concentrations were determined by previous pilot studies on other rats). When the contractions were stable, increasing concentrations of acetylcholine were cumulatively added to the baths. In each segment, the responses of the different concentrations of acetylcholine were expressed as percentages of the agonist-induced contraction obtained before acetylcholine was added. Half of the ring segments from the grafts and from the normal vessels served as internal controls to which no addition of acetylcholine was made.

Acetylcholine was chosen as the most sensitive endothelium-stimulating drug of several to demonstrate an impairment of EDRFs; Vanhoutte's group [18] found that acetylcholine loses its ability to induce endothelium-dependent relaxation in autogenous femoral veins grafted into the arterial circulation of the dog, whereas the other test substances used maintained this ability.

Preparation for Scanning Electron Microscopy

When the bath experiments were fulfilled, the Krebs solution was replaced by a fixation solution consisting of one part 25% glutaraldehyde and ten parts Millonig's phosphate buffer (containing 0.54% glucose; pH 7.3). This procedure was followed to obtain fixation in the stretched condition (ie, at approximately basal tension). After 2 hours, the specimens were removed from the baths and kept in the same fixative in a refrigerator (4°C) for 12 hours. Then the specimens were rinsed four to five times in Millonig's buffer and dehydrated in increasing concentrations of alcohol and dried at the critical point. They were mounted on holders and coated with gold-palladium. The specimens were examined in a Jeol T 330 scanning electron microscope and photographed at different magnifications.

Histology

Some specimens were fixed in 4% phosphate-buffered (pH 7.0) formalin-saline solution. Then they were sectioned and stained with hematoxylin and eosin.

Statistical Analysis

The Mann-Whitney U test was used for statistical comparisons. A probability level of less than 0.05 was regarded as significant.

Results

All grafts were patent after 3 days (n = 2) and 60 days (n = 6).

Structural Changes in the Grafts

In the 60-day grafts, histological study showed the pattern of elastomuscular arteries without intimal thickening and a media consisting of eight to ten muscle layers interrupted by five to six elastic lamellae (Fig 1). Scanning electron microscopy showed no major differences between normal endothelium and the endothelium of 3-day or 60-day grafts (Figs 2, 3).

Effect of Acetylcholine on Normal Aortic Vessels

Acetylcholine induced both concentration-dependent and endothelium-dependent relaxation in aortic segments in-

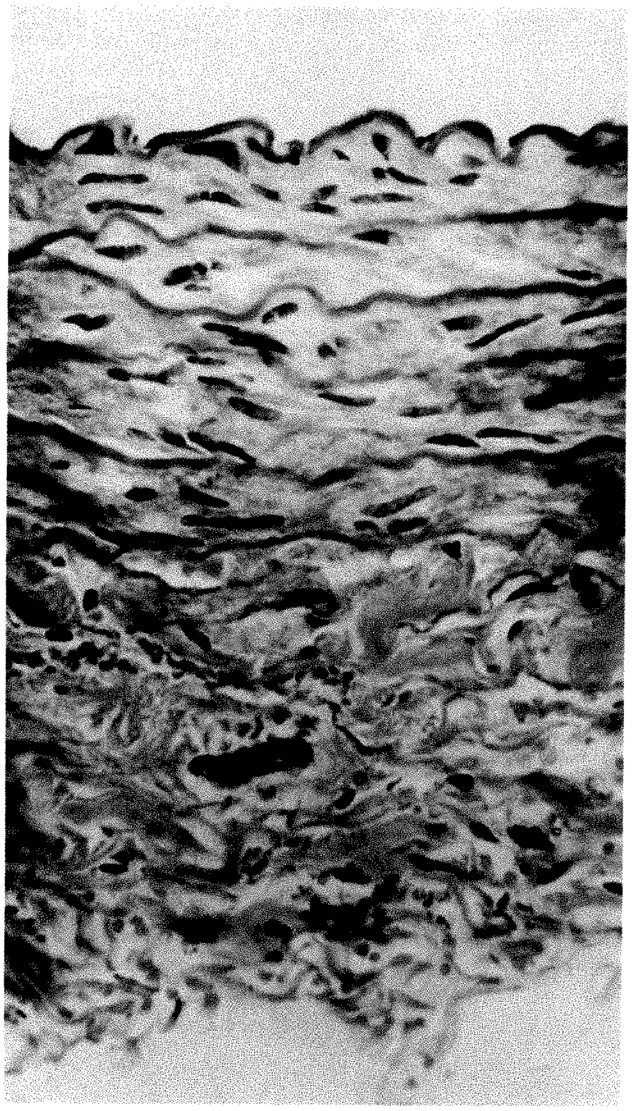


Fig 1. *Photomicrograph of an aortic graft 60 days after transplantation. The luminal side of the vessel is at the top. No intimal thickening can be seen. The media (about 100 µm thick) consists of eight to ten muscle layers interrupted by five to six elastic lamellae. (Hematoxylin and eosin; ×350 before 3% reduction.)*

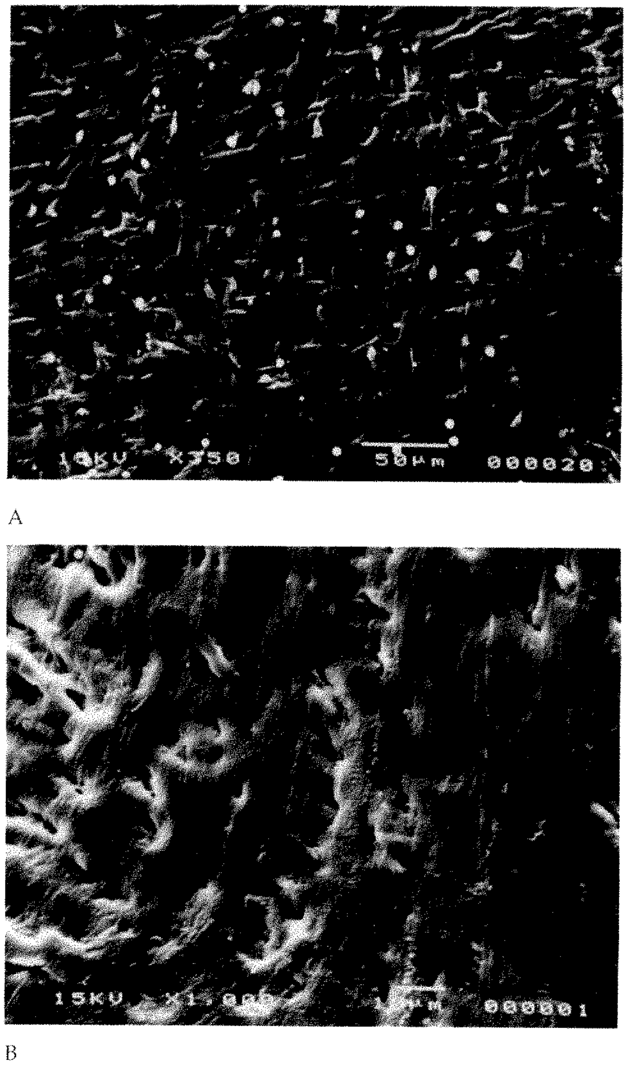


Fig 2. *(A, B) Scanning electron micrographs of a 3-day aortic graft. The axis of the vessel (blood flow) is vertical. Protruded endothelial nuclei lying in the direction of flow can be seen. (A, ×350; B, ×1000; both before 20% reduction.)*

dependently whether contractions were induced with $PGF_{2\alpha}$ (Fig 4), U-46619 (Fig 5), or noradrenalin (Fig 6). The effect of acetylcholine was biphasic; the lowest concentrations (10^{-8} to 10^{-5} mol/L) induced concentration-dependent relaxation up to 16% ± 3% ($PGF_{2\alpha}$), 17% ± 4% (U-46619), and 24% ± 11% (noradrenalin) of the contractile force (defined as 100%) before acetylcholine was added. Higher concentrations of acetylcholine (10^{-5} to 10^{-3} mol/L) increased the tension again from approximately 20% to about 40% of the initial contraction. Acetylcholine did not induce any relaxation in vessels without endothelium previously constricted with $PGF_{2\alpha}$ (see Fig 4), U-46619, or noradrenaline. Nor did the control segments constricted with $PGF_{2\alpha}$ (see Fig 4), U-46619, or noradrenaline (ie, segments not exposed to acetylcholine), with or without endothelium, significantly change their tension over the time needed to obtain the concentration–response curves with acetylcholine.

Effect of Acetylcholine on 60-Day Free Aortic Grafts

When U-46619 was used as the contraction-inducing agent, acetylcholine showed almost identical relaxing properties as in normal aortic ring segments (see Fig 5). The remaining minimum contraction in the graft segment was 16% ± 4%. To get stable contractions with noradrenaline, the concentration had to be 100 times higher in the graft (10^{-5} mol/L) compared with the normal aortic segments (10^{-7} mol/L) (see Fig 6). Acetylcholine induced relaxation in the noradrenalin-contracted graft segments (remaining minimum contraction, 39% ± 6%) that was not significantly different from that in normal segments (24% ± 11%). Acetylcholine had no effect on grafts without endothelium whether they were constricted pre-

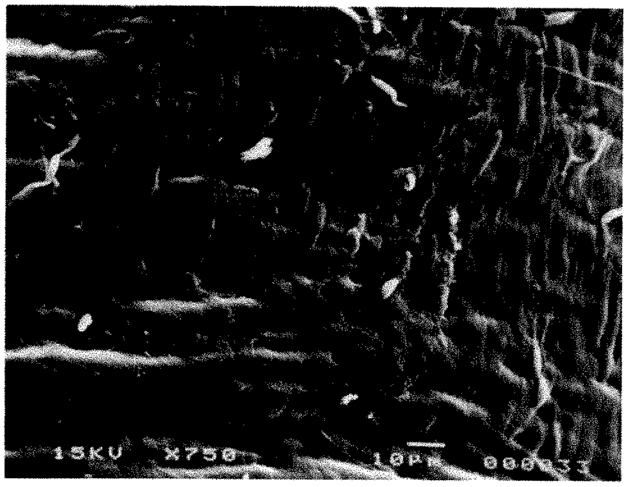


Fig 3. Scanning electron micrograph of a 60-day aortic graft. The axis of the vessel (blood flow) is vertical. Protruded endothelial nuclei can be seen. (×750 before 20% reduction.)

viously with U-46619 (Fig 7, lower panel) or noradrenaline.

Effect of Acetylcholine on 3-Day Free Aortic Grafts

Two grafts were studied 3 days after the operation. U-46619 and noradrenaline were used as constricting agents. In these grafts, acetylcholine exerted the same biphasic (relaxation followed by contraction) effect as in the other grafts (Fig 8, lower panel). The maximal relaxing values were on the same order as in the 60-day grafts.

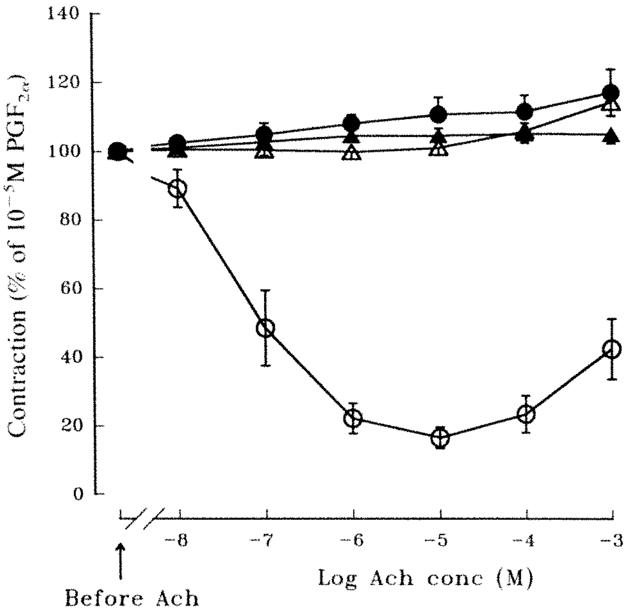


*Fig 4. Effect of acetylcholine (*Ach*) on fresh rat aorta previously constricted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Each point in the curves indicates the mean ± the standard error of the mean (n = 6). (○——○ = fresh aorta with endothelium exposed to acetylcholine; △——△ = fresh aorta without endothelium exposed to acetylcholine; ●——● = controls with endothelium not exposed to acetylcholine; ▲——▲ = controls without endothelium not exposed to acetylcholine;* conc *= concentration.)*

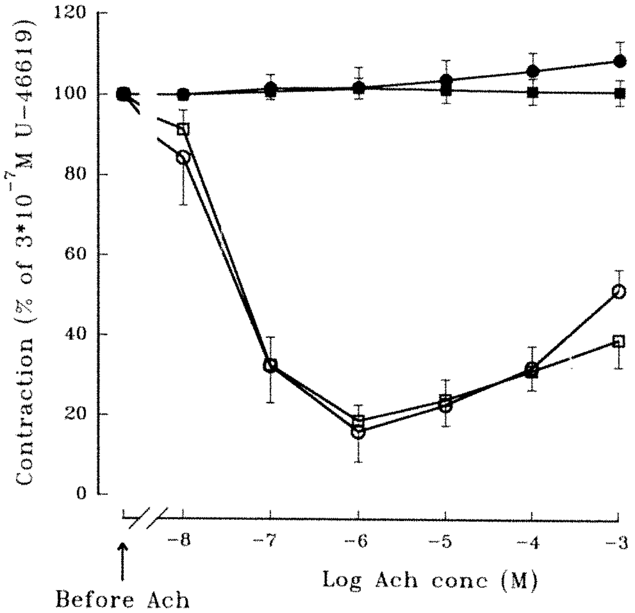


*Fig 5. Effect of acetylcholine (*Ach*) on 60-day grafts and fresh rat aorta previously constricted with U-46619. Each point in the curves indicates the mean ± the standard error of the mean (n = 6). (○——○ = 60-day grafts with endothelium exposed to acetylcholine; □——□ = fresh aorta with endothelium exposed to acetylcholine; ●——● = controls of 60-day grafts with endothelium not exposed to acetylcholine; ■——■ = controls of fresh aorta with endothelium not exposed to acetylcholine;* conc *= concentration.)*

Comment

This study compares the function of EDRFs in arterial grafts with their function in normal control vessels. In U-46619–constricted vessel segments, the acetylcholine curves of the grafts and of the normal control vessels overlapped each other (see Fig 5). This indicates that the endothelium of the grafts has retained a full capacity to release EDRFs. The difference (although it was not significant) between the acetylcholine curves in noradrenaline-contracted vessels (see Fig 6) can probably be explained by a change in the research protocol: the concentration of noradrenaline used in the graft segments had to be 100 times higher than in the normal control segments to get stable contractions over the time needed to obtain the acetylcholine concentration–response curves. This is also reflected by the difference (although not significant) between the controls for the two types of vessels (see Fig 6). The results of the present study therefore indicate that the endothelium in the grafts completely maintained its ability to produce EDRFs.

By use of inbred animals immunologic reactions, and thereby rejection of the transplanted tissue, are avoided. A cold (4°C) Krebs buffer solution was used as the preservation solution because we have found that fresh rat aortas can be kept in this solution for several hours

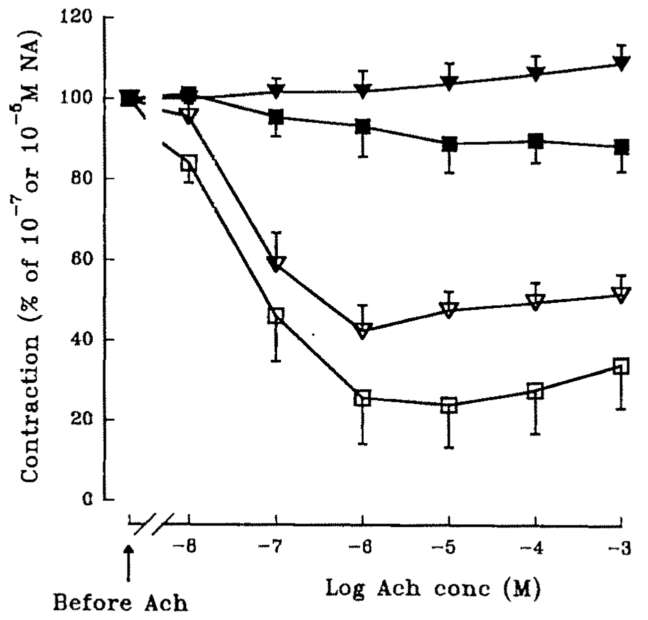


Fig 6. Effect of acetylcholine (Ach) *on 60-day grafts and fresh rat aorta previously constricted with noradenaline* (10^{-5} *mol/L and* 10^{-7} *mol/L, respectively). Each point in the curves indicates the mean ± the standard error of the mean (n = 6).* (▽——▽ *= 60-day grafts with endothelium exposed to acetylcholine;* □——□ *= fresh aorta with endothelium exposed to acetylcholine;* ▼——▼ *= controls of 60-day grafts with endothelium not exposed to acetylcholine;* ■——■ *= controls of fresh aorta with endothelium not exposed to acetylcholine;* conc = *concentration.)*

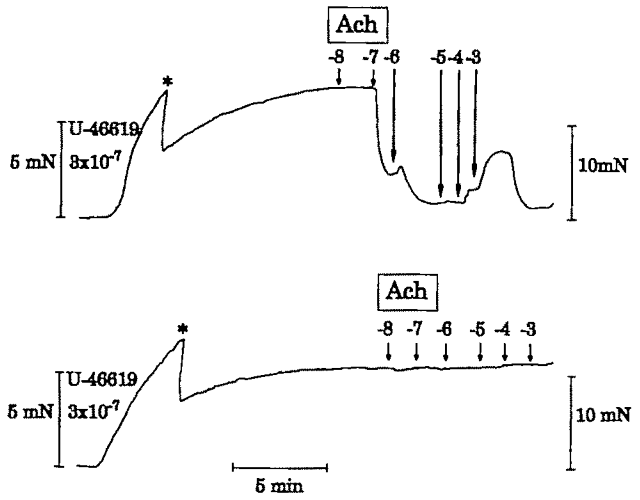


Fig 7. Tracings from two acetylcholine (Ach) *concentration–response curves for U-46619–contracted graft segments taken from the same rat 60 days after the operation. The upper curve shows the effect on a graft segment with endothelium and the lower curve, a graft segment without endothelium. The* asterisk *indicates a change in the sensitivity of the amplifier. The scale of the ordinate before and after the change in the sensitivity is shown to the left (5 mN) and right (10 mN). Acetylcholine concentrations are given as logarithmic concentrations in moles per liter.*

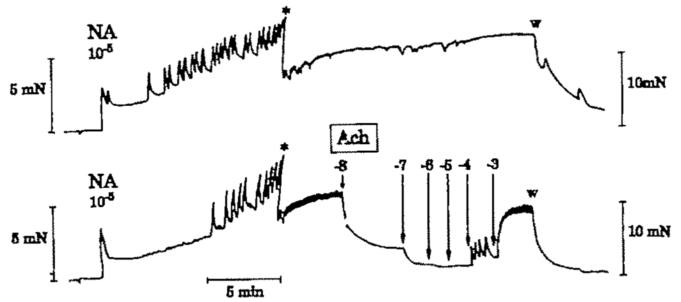
without loosing the ability to release EDRFs from the endothelium (unpublished observations). Christie and co-workers [19] found that storage in either heparinized Hartmann's solution or heparinized whole blood results in diminished release of EDRFs.

In the present study, the endothelium of the 60-day grafts is most likely the original endothelium. This is shown by the experiments done 3 days after the operation, ie, at an interval too short for the appearance of a new, regenerated endothelium. Scanning electron microscopy revealed an almost intact endothelium, and the functional studies showed that the endothelium had preserved its ability to release EDRFs after exposure to acetylcholine. Vanhoutte's group [20] found that regenerated endothelial cells lose the ability to release EDRFs in response to certain stimuli.

The patency of the transplanted aortic grafts in this study was 100%. In an earlier study [21] of rat femoral artery used as a free graft, the patency after 2 days was 100%, but after 60 days it was only 18%. The rat femoral artery is a muscular artery, whereas the infrarenal aorta of the rat is an elastomuscular artery (see Fig 1). The possible importance of morphological differences between various arteries used as free grafts has been pointed out by van Son and associates [22]. In the rat femoral artery used as a free graft, intimal thickening was occurring, but in the present study, no intimal thickening was observed. Clinical observations [23, 24] have indicated that the internal mammary artery, which is a thin-walled elastomuscular artery, is more suitable as a free graft than the radial artery, which is a thick-walled muscular artery.

Whether intimal thickening in free arterial grafts will

Fig 8. Tracings of the effect of acetylcholine (Ach) *on noradrenaline* (NA)*-contracted aortic graft segment. Both segments are taken from the same rat 3 days after the operation. The upper curve shows the control segment contracted during the same period in which the concentration–response curve with acetylcholine was obtained. The lower curve shows the biphasic effect of acetylcholine. The * indicates a change in the sensitivity of the amplifier. The scale of the ordinate before and after the change in the sensitivity is shown to the left (5 mN) and right (10 mN). Acetylcholine concentrations are given as logarithmic concentrations in moles per liter.*



affect the release of EDRFs has not yet been investigated. Let us postulate that the release of EDRFs is diminished in arterial grafts with intimal thickening. In this situation, the tendency for platelet adhesion will be insufficiently inhibited by the diminished amount of EDRFs, and accordingly, the platelets will more easily adhere to the hypertrophied intima. Furthermore, the diminished amount of EDRFs will accelerate platelet aggregation. When platelets aggregate, mitogenic substances (eg, platelet-derived growth factors) are released, and these have been suggested as one cause of fibromuscular hyperplasia or atherosclerotic proliferative lesions that may occlude the lumen of the vessel [25].

This study indicates that free arterial grafts, in which the morphology of the intima is preserved (see Figs 2, 3), will retain their full ability to release EDRFs. The excellent patency seen in this study might be an indication that EDRFs play an important role in the success of free arterial grafts.

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Changes in Hemodynamics and Coronary Blood Flow During Left Ventricular Assistance With the Hemopump

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The Hemopump, a catheter-mounted left ventricular assist device, has been demonstrated to be effective in supporting patients with potentially reversible cardiac failure. The mechanism of recovery of the hearts with this device is not fully understood. The effects of the Hemopump on hemodynamics and coronary blood flow with and without myocardial ischemia and failure have been studied in 8 anesthetized open-chest dogs. Coronary blood flow in the left circumflex artery was assessed with an intracoronary Doppler catheter. Myocardial ischemia was induced by ligation of the left anterior descending and diagonal branches. The effects of maximum support were compared with those of minimum support. The effects of the Hemopump varied according to cardiac function. When cardiac dysfunction was mild, the Hemopump support slightly reduced myocardial O_2 demand (assessed by pressure-work index) by volume unloading. When cardiac dysfunction was severe, total bypass was achieved and myocardial O_2 demand decreased by 45%, owing to both volume and pressure unloading. Coronary blood flow was incompletely autoregulated, and the ratio of blood flow to O_2 demand increased.

(Ann Thorac Surg 1992;53:1074–9)

The Hemopump (Nimbus Medical, Inc, Rancho Cordova, CA) is a recently developed, catheter-mounted, temporary left ventricular assist device. It has been used for patients in cardiogenic shock after acute allograft rejection or acute myocardial infarction, and for patients who failed to be weaned from cardiopulmonary bypass [1]. Initial clinical results are encouraging, showing the ability of this pump to facilitate the recovery of the failing hearts. It has also been used for prophylactic left ventricular assistance during high-risk coronary angioplasty [2].

The understanding of the mechanism of recovery of the failing hearts and the change in coronary blood flow under Hemopump support is essential for better patient management, but limited information is available on this subject [3, 4]. With this device, blood is continuously pumped out of the left ventricle into the aorta through a 21F inflow cannula that is positioned in the left ventricle across the aortic valve. Maximum flow of the pump depends on mean aortic pressure (MAP), and is relatively limited (approximately 3.5 L/min at an MAP of 60 mm Hg). These characteristics would make the effects of left ventricular assistance with this device different from those with other left ventricular assist devices. The purpose of the present study was to show the effects of Hemopump support on hemodynamics and coronary blood flow in the presence and absence of myocardial ischemia and failure.

Material and Methods

Animal Preparation

Eight adult mongrel dogs weighing from 20 to 38 kg were anesthetized with intravenous pentobarbital (30 mg/kg), intubated, and mechanically ventilated with 60% oxygen. Anesthesia was maintained with 1% to 2% halothane. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

A Swan-Ganz catheter was placed through the left jugular vein. A left thoracotomy and a median laparotomy were performed. A microtip pressure catheter (Millar PC-350; Millar Instruments, Inc, Houston, TX) connected to a control unit (Millar TC-100) was placed in the left ventricle through the left atrium. Heparin was administered intravenously (1 mg/kg). Under fluoroscopic guidance, the Hemopump was introduced into the left ventricle through a transversal arteriotomy of the infrarenal abdominal aorta. It was the same device as that for human use. A 3F intracoronary Doppler catheter (NuVel 7891; NuMed, Inc, Hopkinton, NY) for coronary blood flow velocity (CBFV) assessment was positioned in the left circumflex coronary artery through a 9F Judkins guiding catheter introduced through a puncture of the abdominal aorta. After the Doppler catheter was positioned, the guiding catheter was withdrawn from the coronary ostium. The Doppler catheter was connected to a 20-MHz

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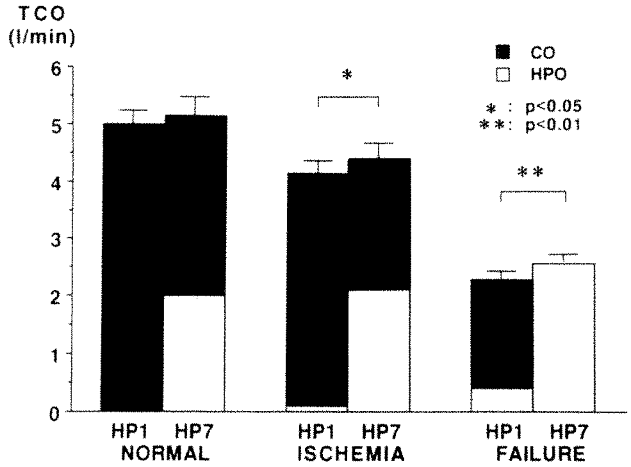


Fig 1. Changes in total cardiac output (TCO) and Hemopump output (HPO). Total height of column represents TCO measured with a Swan-Ganz catheter. In failure, HPO was considered to be equal to TCO, although the estimated HPO exceeded TCO. (CO = cardiac output of the native heart; HP1 = *minimum Hemopump speed;* HP7 = *maximum Hemopump speed.)*

velocimeter (Millar MDV-20). A fluid-filled catheter was placed for aortic pressure measurement.

Experimental Protocol

To avoid movement of the Doppler catheter, the Hemopump cannula was maintained in the left ventricle throughout the experiment. To avoid possible blood regurgitation through the inflow cannula, the Hemopump was actuated at minimum speed (HP1). Therefore the effects of Hemopump support at maximum speed (HP7) were compared with those at minimum speed, and HP1 conditions were considered as control status. Measured parameters were heart rate from the limb lead electrocardiogram, mean and phasic CBFV, mean and phasic aortic pressure, left ventricular pressure and the first derivative, pulmonary artery pressure, and right atrial pressure. All these parameters were recorded on a Gould TA-2000 chart recorder (Gould, Reading, PA). At both pump speeds, total cardiac output was measured with a thermodilution technique. The Hemopump output was indirectly calcu-

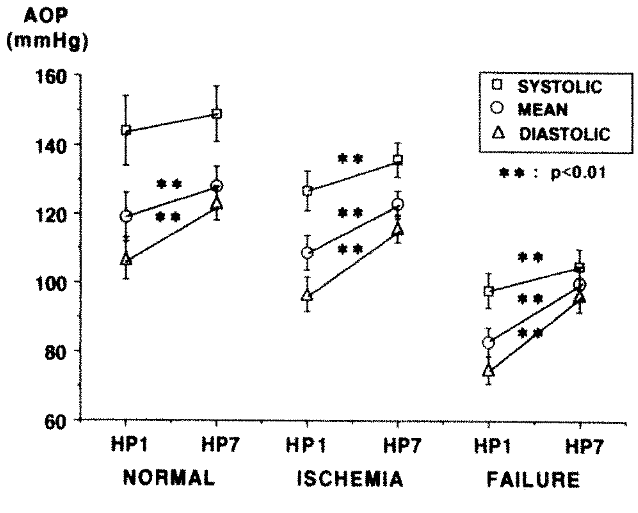


Fig 2. Changes in aortic pressure (AOP). (HP1 = *minimum Hemopump speed;* HP7 = *maximum Hemopump speed.)*

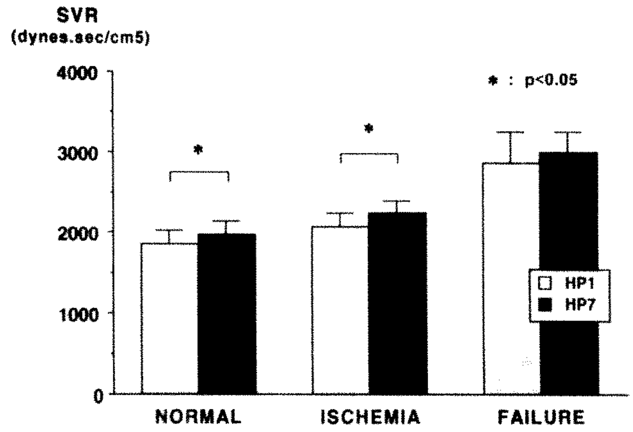


Fig 3. Changes in systemic vascular resistance (SVR). (HP1 = *minimum Hemopump speed;* HP7 = *maximum Hemopump speed.)*

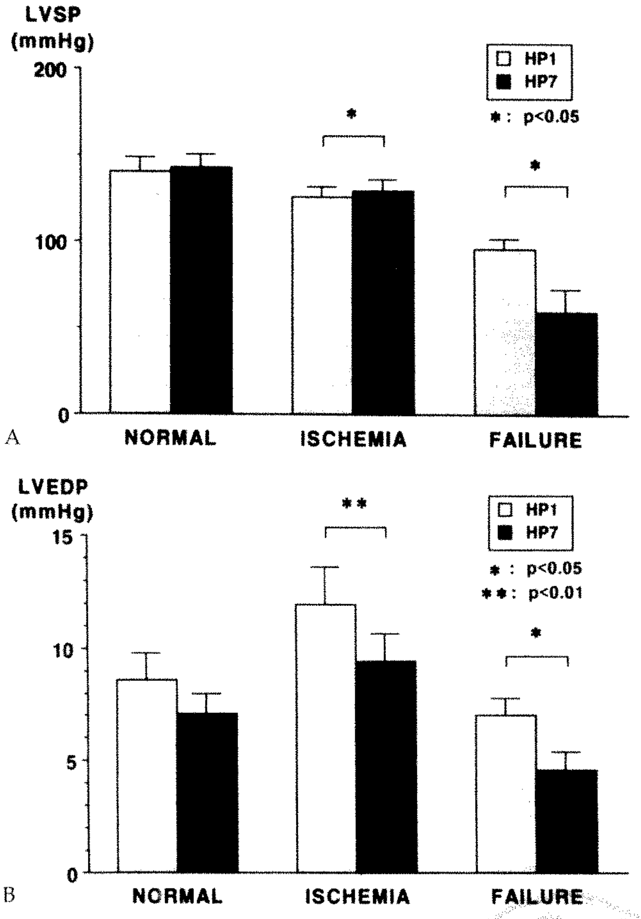


Fig 4. Changes in (A) left ventricular systolic pressure (LVSP) *and (B) end-diastolic pressure* (LVEDP). (HP1 = *minimum Hemopump speed;* HP7 = *maximum Hemopump speed.)*

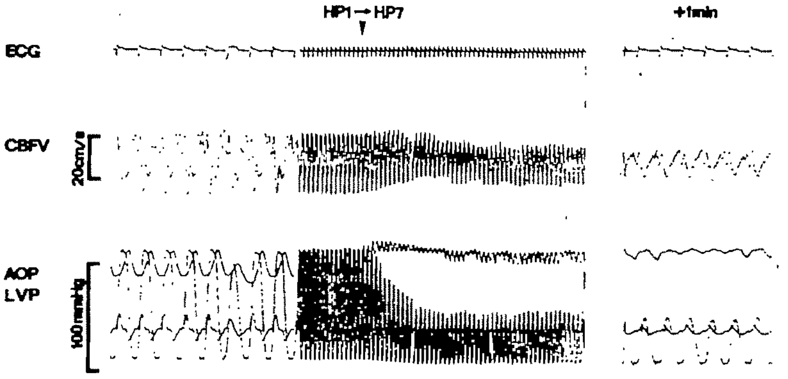


Fig 5. A representative tracing of electrocardiogram (ECG), coronary blood flow velocity (CBFV), aortic pressure (AOP), left ventricular pressure (LVP), and its first derivative in 1 dog. Total cardiac output was 2.53 L/min at HP1. At HP7, AOP increased and separated from LVP, which showed a dramatic decrease. A brief period of increase in CBFV at the moment of change of pump speed preceded the steady state. (HP1 = minimum Hemopump speed; HP7 = maximum Hemopump speed.)

lated by a computerized algorhythm console of the console itself as a function of MAP.

After the measurements for normal heart were completed, the left anterior descending coronary artery after the first diagonal branch was ligated and measurements were repeated. Then ligations of all the visible diagonal branches were added, and measurements were repeated. In 3 dogs, additional measurements were made after further ligations of the proximal left anterior descending coronary artery (all 3 dogs) and, subsequently, a few proximal marginal branches (2 of 3 dogs). Thus three to five pairs of measurements were made for each dog. Before each coronary ligation, 2 mg/kg of lidocaine was administered intravenously. The interval between coronary ligation and measurements was 10 minutes.

Data Analysis

Left ventricular pressure-work index (PWI) according to Rooke and Feigl [5] was used to assess the change in left ventricular myocardial oxygen demand. Their original formula was modified to make it match the experimental condition:

$$MVO_2 = K_1(LVSP \times HR) + K_2[(LVSP - 0.2PP) \times (TCO - HPO)/BW] + K_3$$

where MVO_2 is left ventricular myocardial oxygen consumption (mL $O_2 \cdot min^{-1} \cdot 100\ g^{-1}$), LVSP is left ventricular systolic pressure (mm Hg), HR is heart rate (beats/min), PP is pulse pressure (mm Hg), TCO is total cardiac output (mL/min) measured by thermodilution technique, HPO is Hemopump output (mL/min), and BW is body weight (kg). The coefficients are: $K_1 = 4.08 \times 10^{-4}$, $K_2 = 3.25 \times 10^{-3}$, $K_3 = 1.43$. We also analyzed the two essential components of PWI independently, namely, systolic pressure rate product (PRP = LVSP × HR) and left ventricular external work (LVEW = (LVSP − 0.2PP) × (TCO − HPO)/BW).

Statistics

The data were expressed as mean ± standard error of the mean. Statistical analyses were performed with Student's paired *t* test between data at HP1 and those at HP7. Values of *p* less than 0.05 were considered to be significant.

Results

Total cardiac output in the control condition was 4.99 ± 0.25 L/min in normal hearts (group normal), 3.86 ± 0.45 L/min after ligation of the LAD, 3.29 ± 0.44 L/min after ligations of the diagonal branches, and 3.33 ± 0.39 L/min after further ligations. Because the effect of each coronary ligation on TCO varied considerably among individual dogs, we divided the data after coronary ligation into two groups according to TCO: those in which TCO was greater than 2.99 L/min (ischemia group) and those in which TCO was less than 2.99 L/min (failure group). The borderline value was decided as the mean minus 3 times the standard deviation (lower limit of 99% confidence area) of TCO in normal hearts. As a result, 14 pairs of measurements in 7 dogs were included in the ischemia group and 7 pairs of measurements in 6 dogs were included in the failure group. Total cardiac output at HP1 was 4.13 ± 0.23 L/min in the ischemia group and 2.28 ± 0.16 L/min in the failure group.

Effects on Hemodynamics

Support at HP7 resulted in a significant increase in TCO in the ischemia and failure groups, whereas no significant change was seen in the normal group. The contribution of Hemopump output to TCO (assist ratio) at HP7 was 40% ± 3% in the normal group and 51% ± 4% in the ischemia group. In the failure group, this ratio was 104% ± 6%; it was more than 87% in an individual dog (Fig 1).

Mean aortic pressure showed a significant increase in all three groups at HP7. This increase was due to an increase of diastolic blood pressure in the normal group, whereas both systolic and diastolic pressures showed a significant increase in the ischemia and failure groups (Fig 2).

Systemic vascular resistance showed an increase at HP7 in all three groups, and the difference was significant in the normal and ischemia groups (Fig 3).

Figure 4 shows the change in left ventricular pressures. Left ventricular systolic pressure did not show a significant change in the normal group, whereas it showed a significant increase at HP7 in the ischemia group. These changes corresponded to the changes in systolic blood pressure. By contrast, LVSP in the failure group showed a dramatic decrease at HP7, and separated from aortic

Table 1. Changes in Right Atrial Pressure, Mean Pulmonary Arterial Pressure, and Total Pulmonary Resistance^a

	Normal		Ischemia		Failure	
Variable	HP1	HP7	HP1	HP7	HP1	HP7
RAP (mm Hg)	4.6 ± 1.0	4.5 ± 0.9	5.1 ± 0.7	5.2 ± 0.7	5.4 ± 1.2	5.1 ± 1.1
MPAP (mm Hg)	18 ± 2	18 ± 2	16 ± 1	17 ± 1	16 ± 2	16 ± 2
TPR (dynes · s/cm^3)	299 ± 45	291 ± 45	332 ± 36	318 ± 30	598 ± 139	510 ± 95

^{a} No difference between HP1 and HP7 was statistically significant.

HP1 = minimum Hemopump speed; HP7 = maximum Hemopump speed; MPAP = mean pulmonary arterial pressure; RAP = right atrial pressure; TPR = total pulmonary resistance, calculated as (MPAP/total cardiac output) × 79.92.

pressure (Fig 5). Left ventricular end-diastolic pressure showed a decrease at HP7 in all three groups, and the difference was significant in the ischemia and failure groups.

None of right atrial pressure, mean pulmonary arterial pressure, or total pulmonary resistance showed a significant change in any of the three groups (Table 1).

Effects on Myocardial Oxygen Demand and Coronary Blood Flow Velocity

In the normal and ischemia groups, LVEW showed a significant decrease at HP7, whereas PRP did not show a significant change. Net change in PWI in these groups was a slight but significant decrease. In the failure group, both PRP and LVEW showed a significant decrease at HP7 (Table 2).

Figure 6 represents a comparison of the percentage decrease of LVEW, PRP, and PWI from values at HP1 according to assist ratio. Left ventricular external work showed a linear decrease according to increase in assist ratio, whereas PRP did not show any relationship, and decreased only when the assist ratio approached 100%. Therefore, net change in PWI was nonlinear.

Mean CBFV did not show a significant change, despite an actual increase of coronary perfusion pressure due to an increased mean or diastolic aortic pressure. However, the ratio of mean CBFV to PWI showed a significant increase at HP7 in all three groups (Table 3).

Comment

In the present study, we could demonstrate that the effects of the Hemopump assist vary according to the condition of the native heart before assist. In the normal heart, the Hemopump reduced LVEW by decreasing stroke volume and increased diastolic aortic pressure, whereas TCO remained unchanged. In the presence of mild cardiac dysfunction induced by coronary ligations (group ischemia), TCO showed an increase, which was accompanied by an elevated MAP and LVSP, whereas LVEW decreased. In the presence of ischemic cardiac insufficiency (group failure), Hemopump assist increased TCO and MAP, and decreased LVEW. Left ventricular systolic pressure and PRP showed a decrease only in this condition.

According to these differences, the mechanism and degree of the reduction of left ventricular myocardial oxygen demand (assessed by PWI) were different between groups. In the normal and ischemia groups, the reduction of oxygen demand was due to a reduction of LVEW caused by reduced stroke volume (volume unloading). But this reduction in volume load was not accompanied by a reduction in PRP, presumably because of an increased systemic vascular resistance due to nonpulsatile flow. Consequently, net reduction of PWI was small (−15%). In group failure, the reduction of PWI was due to a reduction of both LVEW and PRP (volume and pressure unloading), and reached −44%.

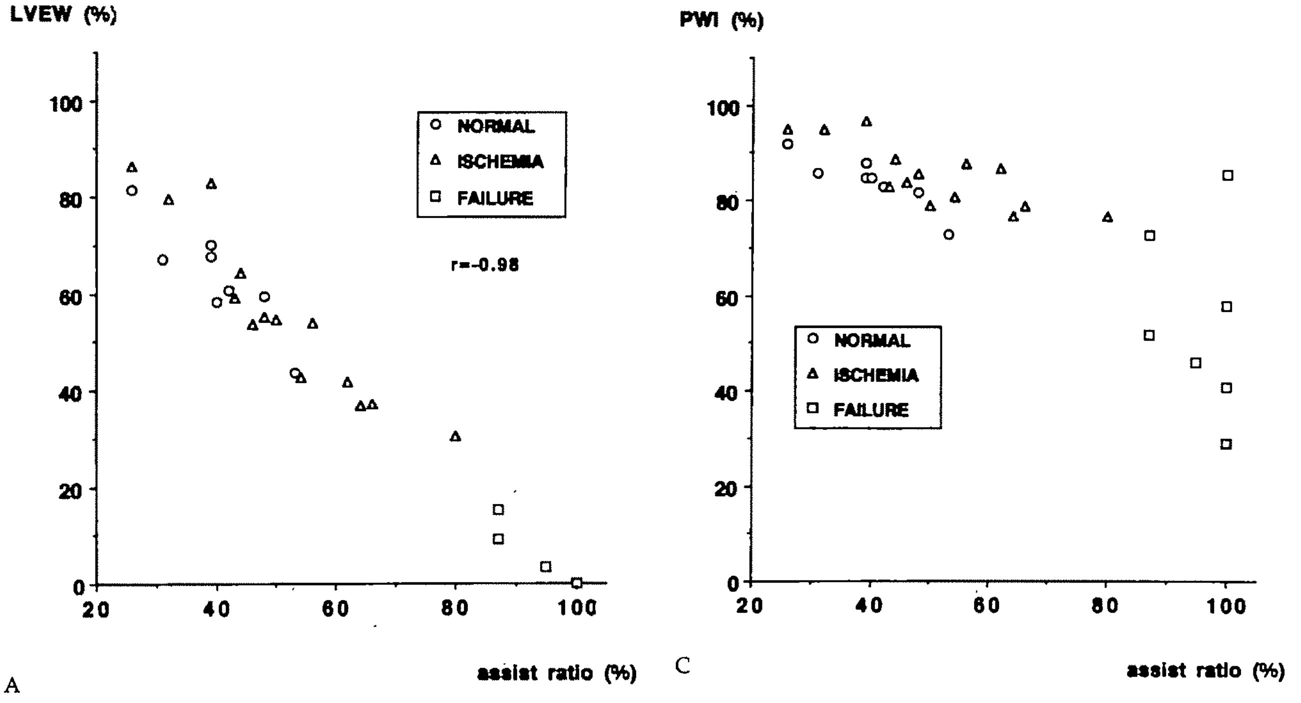
These differences are presumably due to the difference in assist ratio. In the present study, assist ratio remained 40% in the normal group and 51% in the ischemia group because of the limited output of the Hemopump, whereas near-total bypass could be achieved in the failure group because the output of the native heart was lower than this limit. Pierce and associates [6] have shown, using a nonpulsatile pump, that LVSP showed a decrease only

Table 2. Changes in Left Ventricular External Work, Pressure–Rate Product, and Pressure–Work Index

	Normal		Ischemia		Failure	
Variable	HP1	HP7	HP1	HP7	HP1	HP7
LVEW (mm Hg · mL · min^{-1} · kg^{-1})	21,348 ± 2,102	13,995 ± 2,065^a	15,257 ± 1,395	9,068 ± 1,345^a	5,773 ± 703	278 ± 169^a
PRP (mm Hg/min)	20,437 ± 1,739	19,860 ± 1,349	16,828 ± 969	17,206 ± 1,003	12,726 ± 1,122	8,007 ± 2,097^b
PWI	16.7 ± 1.0	14.1 ± 0.9^a	13.3 ± 0.7	11.4 ± 0.7^a	8.5 ± 0.5	4.8 ± 0.9^a

^{a} $p < 0.01$, ^{b} $p < 0.05$ versus HP1.

HP1 = minimum Hemopump speed; HP7 = maximum Hemopump speed; LVEW = left ventricular external work; PRP = systolic pressure–rate product; PWI = pressure–work index.



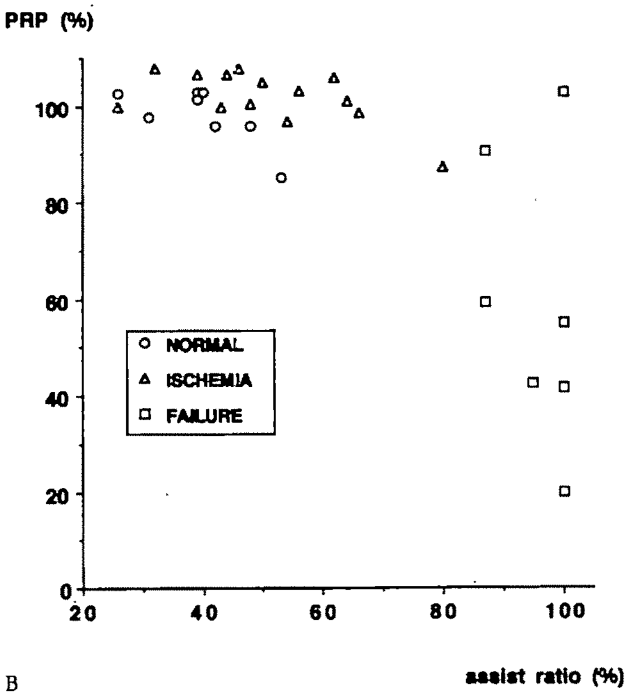


Fig 6. Comparison of the percentage decrease of (A) left ventricular external work (LVEW), (B) systolic pressure–rate product (PRP), and (C) pressure–work index (PWI) from values at the minimum Hemopump speed according to assist ratio.

when total left ventricle-to-aortic bypass is achieved, and myocardial oxygen consumption showed 47% decrease in this condition. The result of the present study is consistent with their result. Pennock and associates [7] have demonstrated a nonlinear relationship between percentage reduction in myocardial oxygen consumption and percentage of bypass using left ventricle-to-aortic nonpulsatile flow bypass, which is similar to our result presented in Figure 6. Therefore the effect of the Hemopump on oxygen demand seems to be essentially the same as that of nonpulsatile left ventricle-to-aortic bypass when assist ratio is comparable.

Several investigators have demonstrated critical importance of left ventricular decompression in reducing myocardial infarct size [8] or in reducing reperfusion injury [9]. Therefore, if we use the Hemopump in an attempt to salvage a jeopardized myocardium, the result of the present study (ie, left ventricular decompression was achieved only when the function of native heart was considerably bad) will have real importance. In the present study, Hemopump output at HP7 remained 2.6 L/min even in the failure group. This is due to high systemic vascular resistance caused by a cut-down of the terminal abdominal aorta for the Hemopump insertion. In the clinical setting, MAP of the patients selected for mechanical assistance would be considerably lower, and a Hemopump output of 3.0 to 3.5 L/min could be expected with the use of vasodilator therapy. Therefore the patients whose cardiac output are lower than this value could be expected to benefit from the use of the Hemopump for this purpose.

The coronary vascular bed has a large capacity to maintain blood flow constant over a wide range of perfusion pressure (coronary autoregulation). The result that CBFV in the nonoccluded vessel did not increase at HP7 despite elevated MAP could be explained by coronary autoregulation. Indeed, we noticed a brief period of

Table 3. Changes in Mean Coronary Blood Flow Velocity and Ratio of Coronary Blood Flow Velocity to Pressure–Work Index

	Normal		Ischemia		Failure	
Variable	HP1	HP7	HP1	HP7	HP1	HP7
CBFV (cm/s)	15.1 ± 1.9	14.5 ± 1.8	14.7 ± 1.7	14.6 ± 1.6	10.2 ± 1.5	9.3 ± 1.3
CBFV/PWI	0.93 ± 0.15	1.07 ± 0.17[a]	1.13 ± 0.12	1.31 ± 0.14[b]	1.20 ± 0.16	1.99 ± 0.31[a]

[a] $p < 0.05$, [b] $p < 0.01$ versus HP1.

CBFV = mean coronary blood flow velocity; HP1 = minimum Hemopump speed; HP7 = maximum Hemopump speed; PWI = pressure–work index.

increase in CBFV at the moment of change of pump speed that preceded the steady state at lower CBFV, both in the present study and in the clinical study [4]. Merhige and associates [3] have shown, using tracer microspheres, decreased myocardial perfusion in the nonischemic area that correlates with reduced fractional shortening caused by Hemopump support. However, the blood flow/O_2 demand ratio (mean CBFV/PWI) showed an increase in the present study, which means that autoregulation was not perfect. Because oxygen consumption is given by the product of blood flow and oxygen extraction, this increase should be accompanied by a reduction in oxygen extraction. Dole and Nuno [10] have demonstrated that reduction of myocardial oxygen consumption attenuates coronary autoregulation. They have concluded that when myocardial oxygen tension is higher than 32 mm Hg, the degree of coronary autoregulation decreases, and an increase in coronary perfusion pressure results in an increase in myocardial blood flow and a decrease in oxygen extraction. The result of the present study is consistent with their result.

Criticism of the Methods

In the present study, we used the PWI of Rooke and Feigl [5] as an index of myocardial oxygen demand. We chose it because it can represent mechanical energy expended for performing external work and maintaining pressure at end-systole, and it does not require the measurement of ventricular volume. An increase in stroke volume with no change in LVSP and HR has been demonstrated to result in an increase in myocardial oxygen consumption [5]. Because similar change could be obtained with left ventricular assistance, use of the index that involves stroke volume is essential. Other indexes that involve an integral over time can account for the oxygen cost of stroke volume, because large stroke volumes are associated with long systolic periods. However, the change in contractility can also change duration of systole. The PWI has been demonstrated to be much less dependent on catecholamine-induced changes in contractility [5].

The application of the PWI to damaged heart remains to be validated, because the damaged heart would certainly have an increased basal metabolic demand. Nevertheless, we believe that use of this index in heart failure is not inappropriate in the sense that the PWI represents total mechanical energy expended by left ventricle.

Conclusion

The results of the present study suggest that: (1) the effects of Hemopump support vary according to the function of the native heart, (2) when cardiac dysfunction is mild, Hemopump support slightly reduces myocardial oxygen demand by volume unloading, (3) when cardiac dysfunction is severe and total bypass is achieved, Hemopump support decompresses the left ventricle and decreases myocardial oxygen demand by 45%, by both volume and pressure unloading, and (4) coronary blood flow in the nonoccluded vessel is incompletely autoregulated, and the ratio of blood flow to oxygen demand increases under Hemopump support.

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Multicenter Clinical Evaluation of the HeartMate 1000 IP Left Ventricular Assist Device

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The Thermo Cardiosystems Inc (Woburn, MA) HeartMate 1000 IP left ventricular assist device (LVAD) has been evaluated as a bridge to transplantation in 34 patients for up to 324 days at seven clinical centers in the United States. Sixty-five percent of the patients underwent transplantation, 80% of whom were discharged from the hospital. Six additional control patients, transplant candidates who met the entrance criteria but who did not receive the device, were also included in the study. Although 3 (50%) of the control patients received transplants, all 6 died within 77 days of having met the LVAD inclusion criteria (100% mortality). Complications resulting from use of the device were comparable with those previously reported for all ventricular assist devices, except for thromboembolic events: bleeding, 39%; infection, 25%; and right heart failure, 21%. No device-related thromboembolic events occurred, although 1 patient experienced an event related to a mechanical aortic valve in the native heart. None of the complications had a significant negative association with outcome of the patient except for right heart failure. All survivors had a significant improvement in hepatic function before transplantation. Total bilirubin values were reduced by 60% during LVAD support. No significant differences were observed when total bilirubin values were compared at 30 and 60 days after LVAD support and at 30 and 60 days after transplantation in a cohort of 15 patients ($p > 0.05$). The improvement in renal function was less predictable than that of hepatic function. Creatinine values decreased significantly before transplantation; however, the values measured at 30 and 60 days after transplantation were higher than those measured at the same intervals after LVAD support had been initiated, and this increase is presumably related to the immunosuppressive drugs. In conclusion, the HeartMate 1000 IP LVAD has been shown to be effective in supporting end-stage cardiomyopathy patients to transplantation. Thromboembolism, previously regarded as a serious complication with such devices, has not been a problem with this device. Additional patients are being enrolled into the study to further document the safety and effectiveness of this technology.

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Although cardiac transplantation has become a widely accepted therapy for patients with end-stage cardiac disease, the demand for donor organs far exceeds the supply [1]. Consequently, a substantial percentage of transplant candidates die while waiting for a donor heart [2, 3]. Temporary mechanical circulatory support for patients waiting for donor organs was introduced by Cooley and co-workers in 1969 [4]. Subsequent research led to the development of ventricular assist devices for use as a bridge to transplantation [5–8]. The results with these devices have been highly encouraging for the support of postcardiotomy [9, 10], postinfarction [11], and end-stage cardiomyopathy patients [12, 13].

Among the currently available left ventricular assist devices (LVADs), two are specifically designed for long-term mechanical circulatory support. Thermo Cardiosystems Inc (Woburn, MA) and Novacor (Oakland, CA) have developed implantable, pusher-plate–type LVADs that are undergoing clinical evaluation under Food and Drug Administration-approved investigational device exemptions [12, 13]. Both devices have been successfully employed as a bridge to transplantation for durations exceeding 10 months, with the majority of patients receiving transplants and achieving long-term survival. The purpose of this report is to summarize the results obtained with one of these devices, the Thermo Cardiosystems Inc HeartMate 1000 IP pneumatically driven LVAD, which has been under evaluation since August 1985.

To extend the use of LVADs to the clinical community, sufficient data must be gathered and presented to the Food and Drug Administration to prove, scientifically, that the device is safe and effective. To be considered safe, the device must be reliable and must not jeopardize the ability to perform transplantation in the patient; that is, the device should not be associated with unacceptable levels of adverse effects, such as infection, bleeding, hemolysis, end-organ dysfunction, or thromboembolic complications. To be considered effective, the device must improve the hemodynamic status of the patient, enhance the likelihood of survival, and, ideally, promote a higher

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quality of life than would be otherwise possible without the device.

The following discussion summarizes data obtained to demonstrate the safety and efficacy of this technology to date.

Material and Methods

Description of the Device

The HeartMate 1000 IP LVAD consists of a pusher-plate blood pump driven by a portable external console via a percutaneous driveline. The pump consists of a titanium housing (titanium, 90%; aluminum, 6%; vanadium, 4%) measuring 11.2 cm in diameter and 4.0 cm in thickness. Inside, a flexible Biomer polyurethane diaphragm is bonded to a rigid pusher plate. The diaphragm divides the pump into two halves: a blood chamber and an air chamber. Programmed pulses of air are delivered from the console to the air chamber behind the pusher-plate diaphragm. As the air accumulates, the diaphragm is displaced, propelling the blood through the outflow graft into the arterial circulation. Porcine xenograft valves (25 mm) are placed in the inlet and outlet conduits to ensure unidirectional blood flow.

Device implantation is accomplished through a median sternotomy, with the incision extending just above the umbilicus, and cardiopulmonary bypass is instituted through standard techniques. The left ventricular apex is cored, and the opening is reinforced with a sewing ring. The pump is then placed in the left abdominal cavity, below the diaphragm. An incision is made in the diaphragm, through which the inlet conduit is passed, then secured to the apical opening. The outflow graft (preclotted Dacron) is passed over the diaphragm and anastomosed end-to-side to the ascending aorta. Finally, the pneumatic drive line is tunneled through a stab incision in the left lateral abdominal wall, above the iliac crest. After the pump has been implanted, the patient is gradually weaned from bypass, and the median sternotomy is closed. A more detailed description of the device and the implant protocol has been published [12].

The portable console, which operates on batteries or standard alternating current power, drives the blood pump directly without the need for tanks of compressed air. Both asynchronous and synchronous control modes of operation are available. The asynchronous modes include fixed-rate and pump-on-full options. If set to operate in the pump-on-full mode, the device will automatically eject when the pump is approximately 90% full. Synchronization of the pump is possible using an external QRS detector.

The combination of an implanted blood pump with a portable external console allows the patient to ambulate and exercise (Fig 1). Patients are encouraged to begin an exercise program consisting of walking and stationary bicycling as soon as possible after implantation to improve their general physiologic status before transplantation.

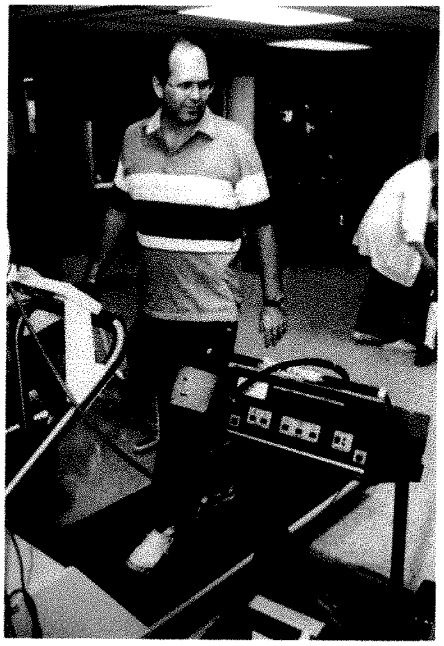

Fig 1. Patients are encouraged to begin ambulating and exercising as soon as possible after LVAD implantation to improve their physiological status before transplantation.

Blood-Contacting Surfaces and Recommended Anticoagulation

The HeartMate LVAD employs textured biomaterials to interface with the blood. Sintered-titanium microspheres are used on the pump housing and conduits, and integrally textured polyurethane is used on the flexing pusher-plate diaphragm. The rationale for using textured surfaces is to encourage the formation of a thin, well-adhered, pseudointimal lining on the inside of the pump. The resultant biologic lining serves as the primary interface with the blood throughout implantation.

The need for anticoagulation with this device has been greatly reduced by use of porcine bioprosthetic valves in combination with the textured surfaces. In the majority of patients, an antiplatelet regimen consisting of 80 mg aspirin, once a day, and 75 mg dipyridamole, three times daily, has been used beyond the intraoperative period. Heparin, sodium warfarin (Coumadin), or both have been used only during implantation and in patients with mechanical valves in the native heart.

Patient Selection

Use of the device was limited to approved transplant candidates who met the hemodynamic indications for use and who were not subject to exclusionary criteria. The hemodynamic indications included a pulmonary capillary wedge pressure of 20 mm Hg or greater coupled with either a cardiac index of 2.0 $L \cdot min^{-1} \cdot m^{-2}$ or less *or* a systolic blood pressure of 80 mm Hg or less. The exclusion criteria included chronic, irreversible hepatic, renal, and respiratory failure; severe blood dyscrasia; and right heart failure. All data were obtained in compliance with proto-

Table 1. Patient Demographics and Results of Treatment with the HeartMate LVAD

Patient No.	Sex	Age (y)	Admission Diagnosis	Implant Duration (days)	Transplanted	Survivor[a] (>60 days)
Patients Who Met the Study Selection Criteria						
1	M	47	Isch CMP	41	Yes	No (liver failure)
2	M	48	Idio CMP	37	Yes	Yes
3	M	17	Viral CMP	7	Yes	No (respiratory failure; adverse OKT3 reaction)
4	M	22	Idio CMP	35	Yes	Yes
5	M	39	Isch CMP	132	Yes	Yes
6	M	43	Idio CMP	114	Yes	Yes
7	M	42	Idio CMP	233	Yes	Yes
8	M	55	Idio CMP	189	Yes	Yes
9	M	41	Idio CMP	31	Yes	Yes
10	M	49	Isch CMP	220	Yes	Yes
11	M	55	Isch CMP	14	No	No
12	M	44	Idio CMP	1	No	No
13	M	55	Idio CMP	61	Yes	Yes
14	M	37	Isch CMP	153	Yes	Yes
15	M	48	Isch CMP	10	No	No
16	M	47	Dil CMP	1	No	No
17	M	47	Idio CMP	38	Yes	Yes
18	M	22	Viral CMP	84	Yes	Yes
19	M	46	Isch CMP	15	Yes	Yes
20	M	57	MI	21	Yes	Yes
21	M	50	Idio CMP	66	Yes	Yes
22	M	39	Dil CMP	6	No	No
23	M	60	Idio CMP	4	No	No
24	M	45	Isch CMP	Ongoing	. . .	. . .
25	M	46	Idio CMP	Ongoing	. . .	. . .
26	F	35	Viral CMP	Ongoing	. . .	. . .
Patients Who Did Not Meet the Study Selection Criteria						
1	M	55	Idio CMP	5	No	No
2	M	53	Idio CMP	19	Yes	No (multiorgan failure, sepsis)
3	M	37	Idio CMP	25	Yes	No (donor heart failure)
4	M	59	Isch CMP	1	No	No
5	M	52	Isch CMP	84	Yes	Yes
6	M	51	Idio CMP	1	No	No
7	M	55	MI	1	No	No
8	M	38	MI	1	No	No

[a] Cause of death appears in parentheses.

CMP = cardiomyopathy; Dil = dilated; Idio = idiopathic; Isch = ischemic; MI = myocardial infarction.

cols approved by the investigational review boards at each of the respective institutions.

Between August 1985 and February 1991, 34 patients at seven medical centers were treated with the HeartMate 1000 IP LVAD as a bridge to transplantation. All but 1 of the patients were male, and their ages ranged from 17 to 62 years.

Of the 34 patients, 26 met the study selection criteria, and 8 did not for various reasons (Table 1). Whereas all 34 patients were considered in the overall evaluation of survival and device safety, only the 26 who met study selection criteria were considered in the analyses of hemodynamic, hematologic, hepatic, and renal response to the pump. Of these 26 patients, 15 were long-term survivors (>60 days) of cardiac transplantation and were discharged from the hospital. Data collection in these patients allowed further comparison of hemodynamic, hematologic, hepatic, and renal values at 30 and 60 days

Table 2. Patient Demographics and Results of Treatment in Six Control Subjects

Patient No.	Sex	Age (y)	Admission Diagnosis	Transplanted	Survivor[a] (>60 days)
1	M	21	Idio CMP	Yes	No (multiorgan failure)
2	M	38	Isch CMP	No	No
3	F	31	PPart CMP	Yes	No (allograft rejection)
4	F	44	Isch CMP	No	No
5	M	52	Isch CMP	Yes	Yes
6	M	57	Isch CMP	No	No

[a] Cause of death appears in parentheses.

CMP = cardiomyopathy; Idio = idiopathic; Isch = ischemic; PPart = postpartum.

of device support and at the same times after transplantation.

Control Population

Six historic controls were entered into the study (Table 2). They were identified by searching the transplant database for candidates who would have met the patient selection criteria for LVAD support but who did not receive treatment with the device because it was not available.

Data Acquisition

Hemodynamic data, including the cardiac index, pulmonary capillary wedge pressure, and blood pressure, were collected. Hematocrit levels, plasma free hemoglobin levels, and platelet counts were monitored to assess the hematologic response to circulatory assistance. Hepatic and renal function were assessed through total bilirubin levels, serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase values, and creatinine and blood urea nitrogen levels. These data were then compared before and during ventricular assistance, as well as after transplantation. The change in New York Heart Association functional status was also assessed before support and at 60 days after transplantation in the 15 patients who survived more than 60 days. Safety data pertaining to the incidence of bleeding, hemolysis, infection, right heart failure, peripheral end-organ failure, and mechanical failure were acquired for all of the patients.

Statistical Analyses

The hemodynamic, hepatic, and renal function entrance criteria were analyzed using nonpaired t tests. Nonpaired t tests were also used to compare hepatic and renal function in survivors and nonsurvivors before and after LVAD treatment. Paired t tests were used to compare LVAD and transplantation data in a sample of 15 patients who were treated with the LVAD and then underwent transplantation. Finally, the survival and complication data were analyzed with the Fisher's exact probability test. A p value of less than 0.05 was considered significant in all analyses.

Results

Evaluation of Device Effectiveness

SURVIVAL DATA. Table 1 lists the age, sex, admission diagnosis, implant duration, and outcome for the 34 LVAD patients. Three of the 34 patients remained on LVAD support at the time of study. Twenty (65%) of the remaining 31 patients received transplants, 16 (80%) of whom were discharged from the hospital. Survival in the 16 patients ranges up to 3 years after the transplant procedure.

Of the 6 control patients, 3 (50%) died before transplantation at 5, 12, and 34 days after having met the hemodynamic indications for LVAD support. The remaining 3 patients underwent transplantation but died at 2, 21, and 77 days after operation. Therefore, all 6 patients died within 77 days of having met the indications for LVAD support, regardless of whether they underwent transplantation. A Fisher's exact probability test revealed that the survival rate of the LVAD-treated group was significantly greater than that of the control group ($p < 0.05$).

HEMODYNAMIC COMPARISON OF THE STUDY GROUPS AT ENTRANCE. The hemodynamic status of the 26 LVAD patients was documented at the time they met the indications for use and within 24 hours before implantation. These data were then compared with the hemodynamic values of the control patients when they met the study entrance criteria. No differences in cardiac index or systolic blood pressures were noted between the LVAD and control patients either at the time of meeting the study entrance criteria or at the time of LVAD implantation ($p > 0.05$). However, the control group had a significantly lower pulmonary capillary wedge pressure than the LVAD group at both points. When the data from the control patients were compared with those of the LVAD patients at the time of implantation, the average hemodynamic values (± the standard deviation) were, respectively, as follows: pulmonary capillary wedge pressure, 23 ± 2 versus 28 ± 8 mm Hg; cardiac index, 1.9 ± 0.8 versus 2.1 ± 0.6 $L \cdot min^{-1} \cdot m^{-2}$; and systolic blood pressure, 90 ± 19 versus 94 ± 19 mm Hg. These data imply that the two groups were hemodynamically comparable, although the control group had a slightly lower wedge pressure.

HEMODYNAMIC PERFORMANCE OF THE LVAD. Figure 2 illustrates the average pump index (pump flow/body surface area) and aortic pressures for the 26 LVAD patients who met the entrance criteria. The average pump index for all patients was 2.86 $L \cdot min^{-1} \cdot m^{-2}$, which was approximately 30% greater than the average cardiac index at the

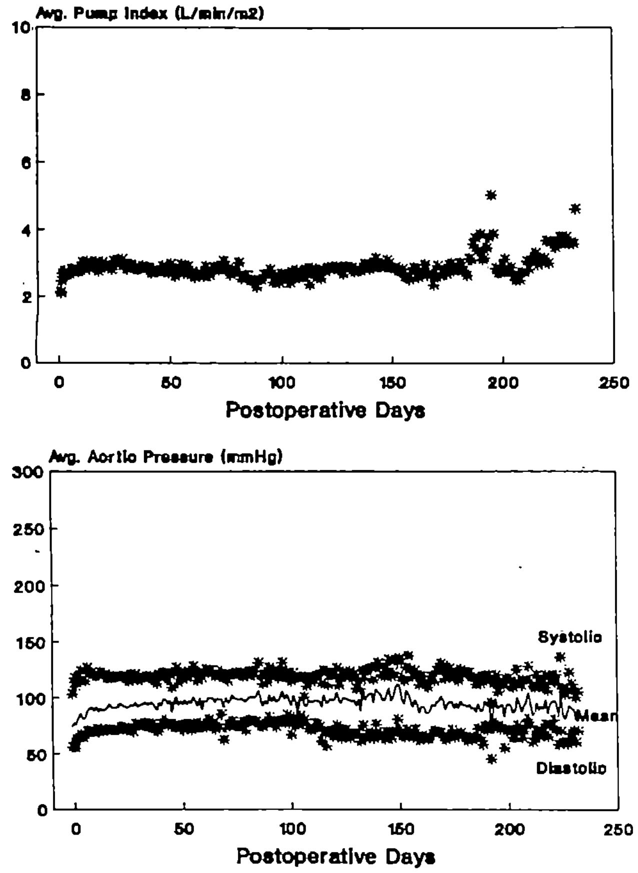

Fig 2. Hemodynamic measurements during LVAD support in 26 patients. The average pump index (pump flow/body surface area) was 2.86 L · min^{-1} · m^{-2}. The average pressures were as follows: systolic, 119 mm Hg; diastolic, 71 mm Hg; and mean pressure, 95 mm Hg.

time of implantation ($p < 0.05$). The systolic, diastolic, and mean aortic pressures were 119 mm Hg, 71 mm Hg, and 95 mm Hg, respectively. The device was found to be fully capable of generating adequate pressures and flows.

EFFECTS OF LVAD SUPPORT ON HEMATOLOGIC INDICES. The average plasma free hemoglobin level was 8.7 mg/dL in the 26 LVAD patients, suggesting that a mild, but clinically acceptable level of hemolysis occurred in these patients (Fig 3). This finding was further confirmed by hematocrit values averaging 34% and platelet counts averaging 249,000/mL. Adequate circulatory support was provided without serious damage to the blood.

EFFECTS OF LVAD SUPPORT ON HEPATIC AND RENAL FUNCTION. All but 2 of the 26 LVAD patients had elevated total bilirubin values (≥1.4 mg/dL) or serum glutamic-oxaloacetic transaminase and/or serum glutamic-pyruvic transaminase values (≥50 U/L) before or during device support. Figures 4 and 5 illustrate the average hepatic values as a function of time. All three parameters tended to increase during the first month, then returned to normal after approximately 2 months of augmented perfusion. The values remained within normal limits for the remaining period of support.

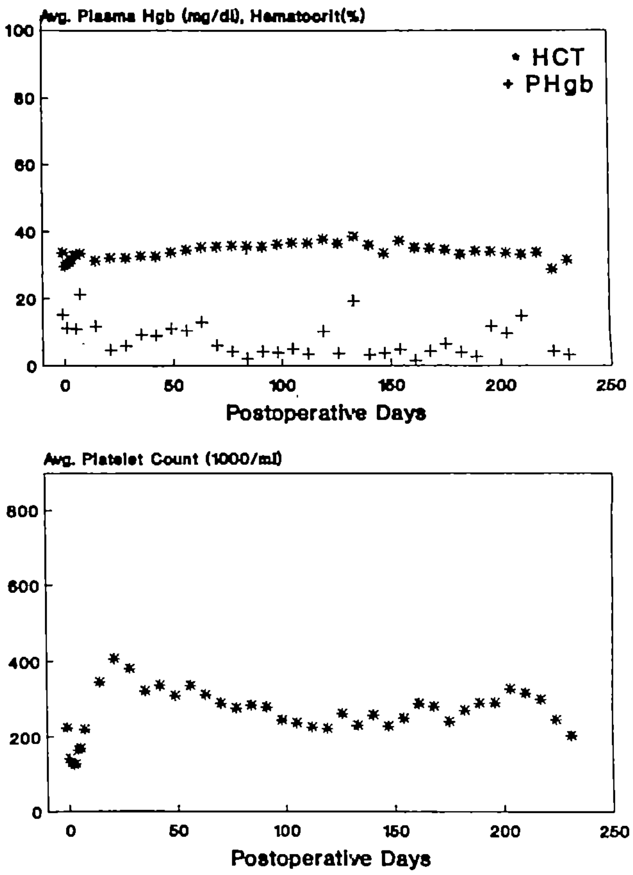

Fig 3. Effects of LVAD support on hematologic indices in 26 patients. Average hematocrit (HCT) was 34%; average plasma free hemoglobin (PHgb) level, 8.7 mg/dL; and average platelet count, 249,000/mL.

Further evidence that hepatic function improved during LVAD support is seen in Figure 6, where the values of total bilirubin before implantation were compared with the final values obtained either just before transplantation or at the time of death. In this analysis, data from 3 of the

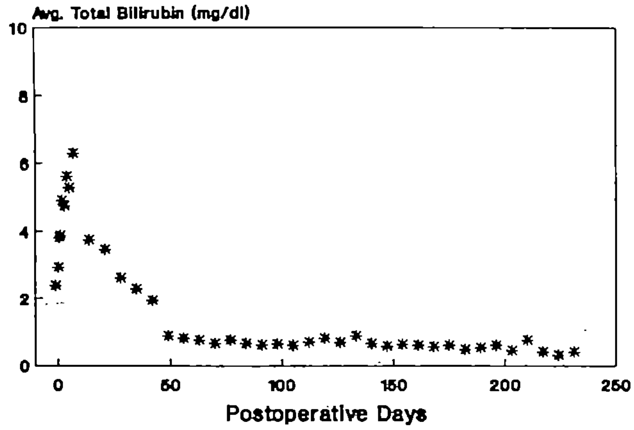

Fig 4. Effect of LVAD support on hepatic function in 26 patients. The average total bilirubin value initially increased, then returned to normal by day 50.

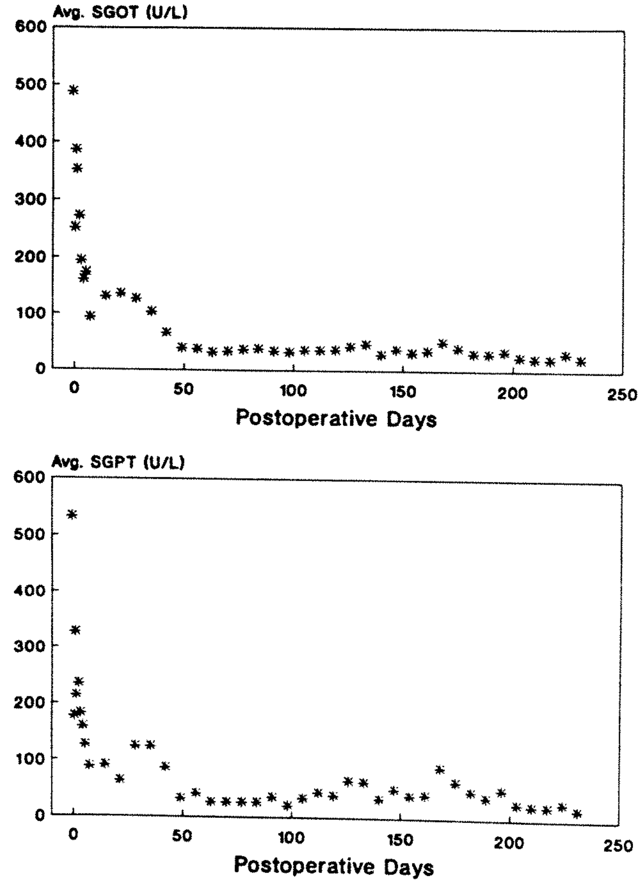

Fig 5. Effect of LVAD support on hepatic function in 26 patients. The serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) values significantly increased during the early postoperative period, then decreased to normal levels by day 50.

patients were excluded because treatment was ongoing. The remaining 23 patients were classified as survivors (n = 15) and nonsurvivors (n = 8). Whereas the total bilirubin values decreased in all survivors, the values either failed to decrease or increased in all nonsurvivors. Hepatic function was improved in all patients with successful transplantations, and 3 patients remained on device support at the time of study.

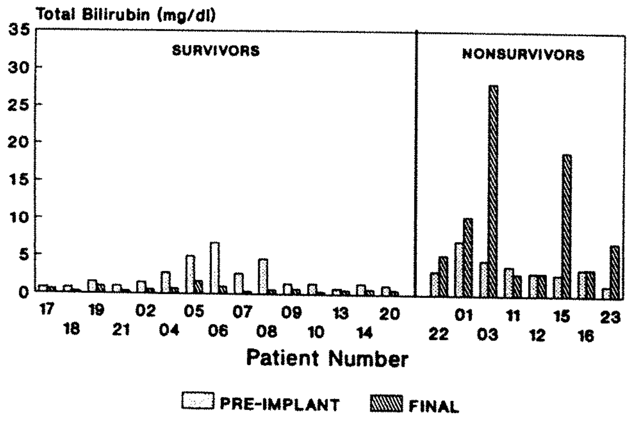

Fig 6. Total bilirubin values were significantly reduced after LVAD support in the survivors. Hepatic function continued to deteriorate in the nonsurvivors despite restoration of blood flow.

The average bilirubin value obtained just before pump removal divided by the baseline value yields a ratio that indicates whether the total bilirubin increased (>1.0), decreased (<1.0), or stayed the same (1.0) in response to the treatment. The bilirubin ratio for the LVAD survivors (0.40) was significantly reduced compared with that of the LVAD nonsurvivors (3.6; $p = 0.03$), as well as the control patients (1.3; $p = 0.004$). In contrast, no significant difference existed between the controls (1.3) and the LVAD nonsurvivors (3.6; $p = 0.09$). These data demonstrate that LVAD support leads to improvement in hepatic function in the majority of patients, providing that dysfunction is reversible.

Hepatic function in the nonsurvivors failed to improve. These patients had significantly higher total bilirubin values at implantation, and the duration of support may have been too short for them to benefit from improved perfusion. The hepatic function of the controls also failed to improve in the absence of mechanical circulatory support.

Figure 7 illustrates the change in serum creatinine and blood urea nitrogen values in response to ventricular assistance. In contrast to the hepatic response, the renal parameters did not transiently increase after LVAD implantation. Moreover, the renal parameters stabilized within a shorter period of time.

COMPARISON OF HEPATIC AND RENAL FUNCTION DURING LVAD SUPPORT AND AFTER TRANSPLANTATION. In a cohort of 15 LVAD patients surviving more than 60 days after transplantation, three hepatic and two renal parameters were measured at LVAD implantation, at days 30 and 60 during support, immediately before transplantation, and at days 30 and 60 after transplantation. A *t* test was then performed to compare the effects of ventricular assistance and transplantation on hepatic and renal function. The only significant difference in hepatic function during LVAD support versus that after transplantation was seen in the total bilirubin level. The LVAD patients had a significantly greater total bilirubin value at implantation compared with that on the day of transplantation.

Figure 8 illustrates the change in total bilirubin values after implantation of the LVAD versus after transplantation. The baseline values ($t = 0$) obtained just before implantation of the LVAD were significantly greater than those obtained just before transplantation ($p < 0.05$). Hepatic function was markedly improved after ventricular assistance, as was the overall physiologic status of the patients before transplantation. No significant differences were noted in the hepatic parameters at days 30 and 60 of LVAD support or at the same times after transplantation.

Figure 9 illustrates the change in renal values as a function of LVAD treatment versus transplantation. The creatinine values were significantly greater before LVAD implantation than before transplantation, demonstrating that the LVAD improved the condition of the patient

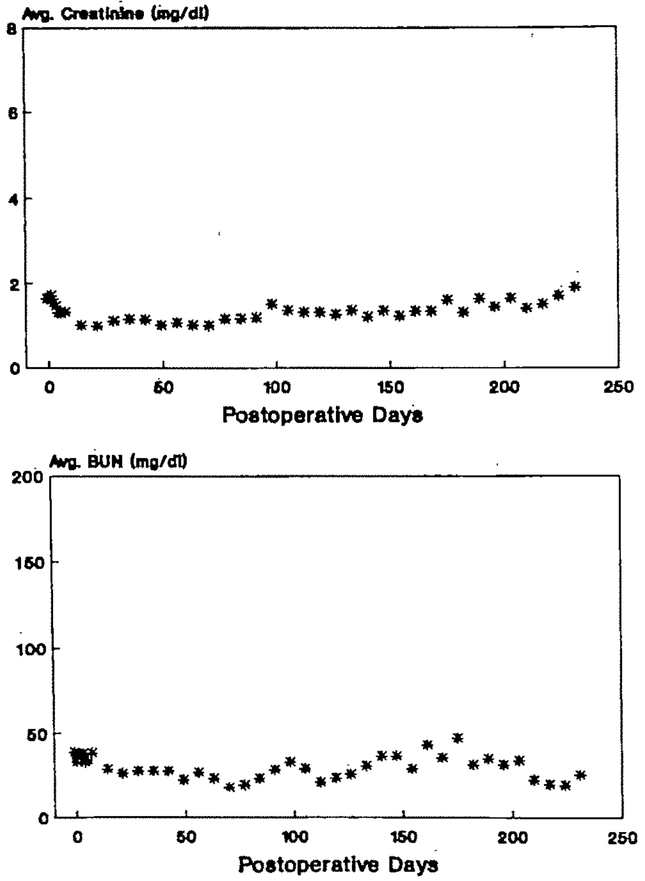

Fig 7. *Effect of LVAD support on renal function in 26 patients. The average creatinine and blood urea nitrogen (BUN) values decreased after implantation and remained within normal limits for the remainder of implant duration.*

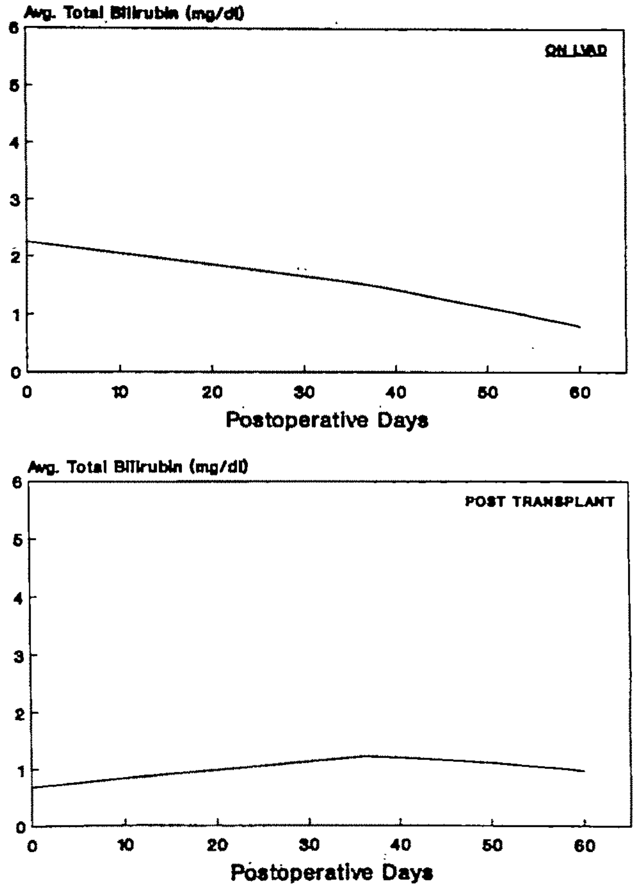

Fig 8. *Comparison of hepatic function after implantation and after transplantation. The average total bilirubin value was significantly greater at LVAD implantation (top) compared with that just before transplantation (bottom) in a cohort of 15 patients. There was no significant difference on days 30 and 60 after each procedure.*

before transplantation ($p < 0.05$). Unlike the hepatic indicators, the creatinine values were significantly elevated at days 30 and 60 after transplantation compared with those at the same intervals after LVAD implantation. The elevated creatinine levels were thought to have been a result of immunosuppressive therapy.

In general, peripheral end-organ function was adequately supported after both LVAD treatment and transplantation. However, the physiologic status of the transplant candidates was markedly improved after LVAD support, enhancing the likelihood of success of transplantation.

Safety Evaluation

A number of risks are associated with the use of ventricular assistance technology. The principal risks currently being monitored include bleeding, hemolysis, infection, right heart failure, peripheral end-organ dysfunction, thromboembolism, and mechanical failure. The frequency and nature of adverse effects resulting from the use of these devices depend on numerous factors, including the basic design of the device, the skill and experience of the clinical team, the physiologic status of the patient, and a multitude of environmental factors that can have a positive or negative impact on the performance of the device.

Adverse effects were monitored for all patients. Of the 34 patients bridged to transplantation, 3 were treated for less than a day and were considered compassionate exemptions, and these patients experienced no adverse effects. Three additional patients remained on LVAD support at the time of study. The safety data reported in this article were collected from the remaining 28 LVAD patients who completed the study. Data are also presented for the six control patients entered into the study. Each category of adverse effects is described in the following sections.

BLEEDING. Bleeding occurred in all of the patients. However, the bleeding was considered serious only if it was severe enough to require returning the patient to the operating room. None of the patients bridged to transplantation experienced device-related bleeding.

Eleven patients (39%) experienced patient-related bleeding, such as that resulting from cardiac tamponade. Seven (64%) of these patients underwent transplantation, 5 (71%) of whom were long-term survivors. Three (50%)

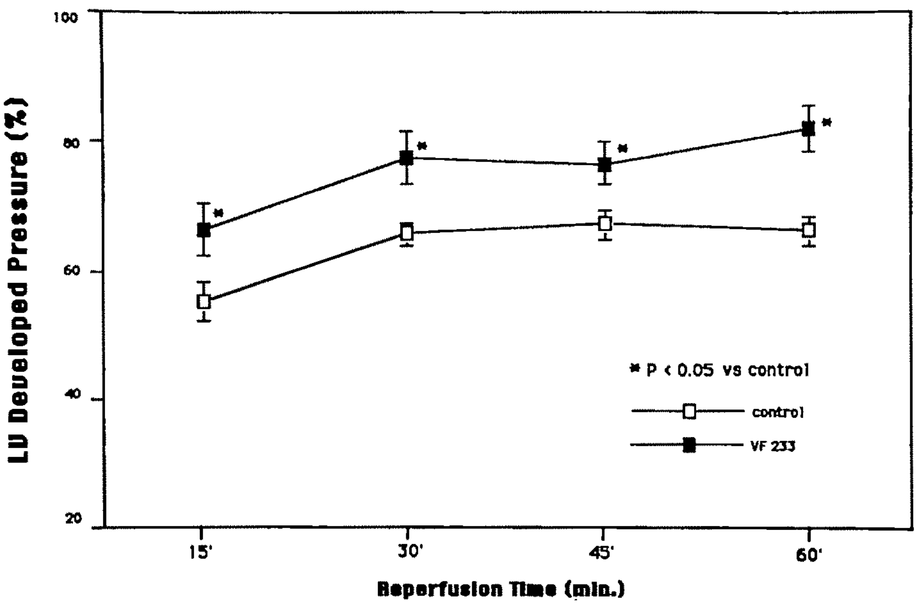

Fig 2. Recovery of left ventricular peak developed pressure (PDP)*, expressed as percent of preischemic control, after 15, 30, 45, and 60 minutes of reperfusion. Recovery of PDP after reperfusion was significantly greater in VF 233–treated than in control hearts* ($p < 0.05$ *by analysis of variance).*

methyl sulfoxide, and deferoxamine have been used as hydroxyl scavengers [18, 19]. Using isolated rabbit hearts subjected to 30-minutes of global ischemia followed by 45 minutes of reperfusion, Ambrosio and associates [19] observed greater recovery of myocardial function with administration of deferoxamine at the time of reperfusion, suggesting that iron plays an important role in free radical–induced myocardial dysfunction. Jackson and coworkers [20] demonstrated that free radicals produced by electrolysis depress left ventricular mechanical function in an isolated rabbit heart model and that this effect was markedly enhanced by iron and attenuated by the OH· scavenger dimethyl sulfoxide.

In the present study, administration of the polyhydroxybenzoic acid derivative VF 233 at the time of reperfusion, followed by continuous infusion during reperfusion, resulted in enhanced recovery of myocardial function (see Fig 2). VF 233 was chosen because it has been demonstrated to possess significant hydroxyl radical scavenging ability in addition to $\cdot\mathrm{O}_2^-$ scavenging ability [21]. The isolated heart preparation was chosen for its precise control of ventricular loading conditions and its ability to control the factors that will affect the heart. Additionally, the use of an isolated heart preparation allowed investigation of myocardial effects of VF 233 independent of its effects on other organ systems. Although these experimental data support the hypothesis that VF 233 improves postischemic left ventricular dysfunction due to a direct effect on myocardial tissue, extrapolation to the clinical setting is limited by the inherent limitations of an isolated

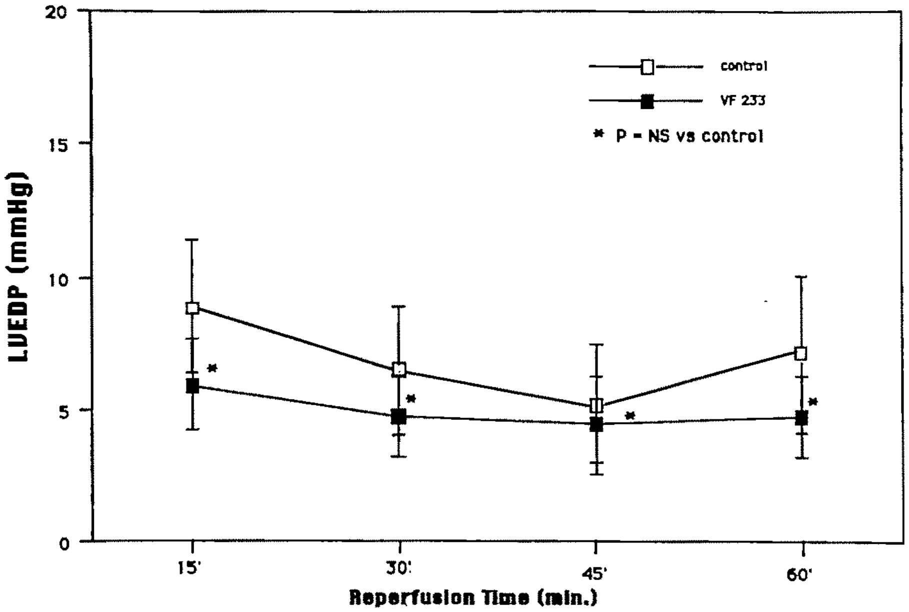

Fig 3. Recovery of left ventricular end-diastolic pressure (LVEDP)*. The time course of recovery of EDP was not significantly different for VF 233–treated versus control hearts* (p *= not significant by analysis of variance).*

Table 1. Effect of VF 233 on Adenine Nucleotide Pool Intermediates[a]

Time	Group	ATP	ADP	AMP	TADN	ADO	INO	TASD	NAD$^+$
Before ischemia	Control	15.02 ± 1.4	9.81 ± 1.1	1.40 ± 1.0	32.54 ± 1.9	0.32 ± 0.4	0.61 ± 0.5	2.65 ± 0.4	3.35 ± 0.3
	Drug	17.35 ± 1.9	11.97 ± 2.1	1.58 ± 1.7	31.65 ± 4.9	0.43 ± 0.1	0.52 ± 0.2	0.95 ± 0.3[c]	3.61 ± 0.5
Ischemia	Control	6.66 ± 1.7[b]	10.0 ± 1.6	7.78 ± 1.2[b]	24.46 ± 1.8[b]	1.51 ± 0.2	5.31 ± 0.8[b]	6.26 ± 0.5[b]	2.39 ± 0.3
	Drug	5.23 ± 0.7[b]	8.28 ± 1.0	5.58 ± 0.8[b]	19.09 ± 1.6[b,c]	1.31 ± 0.4	3.72 ± 0.7[b]	5.03 ± 0.9[b]	2.68 ± 0.6
Reperfusion									
30 min	Control	8.78 ± 1.2[b]	6.42 ± 1.3	3.36 ± 0.7	23.26 ± 2.7[b]	0.79 ± 0.4	2.40 ± 0.8	3.24 ± 0.6	2.91 ± 0.6
	Drug	9.69 ± 0.9[b]	5.86 ± 0.7[b]	4.29 ± 1.3[b]	19.85 ± 1.9[b]	0.84 ± 0.5	0.89 ± 0.4	1.78 ± 0.8	2.65 ± 0.3
60 min	Control	11.87 ± 1.4[b]	6.58 ± 0.9	4.14 ± 0.7[b]	22.59 ± 1.9[b]	0.53 ± 0.1	0.95 ± 0.4	1.37 ± 0.4	3.18 ± 0.4
	Drug	12.10 ± 1.9[b]	6.39 ± 0.8[b]	3.07 ± 0.4[b]	22.06 ± 2.3[b]	0.42 ± 0.1	0.34 ± 0.1	0.75 ± 0.1	3.47 ± 0.5

[a] Data are shown as the mean ± the standard error of the mean, n = 9 for each group. [b] $p < 0.05$ versus baseline. [c] $p < 0.05$ between groups by analysis of variance.

ADO = adenosine; ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; INO = inosine; Ischemia = end of 4 mm Hg ischemia contracture; NAD$^+$ = nicotinamide adenine dinucleotide; TADN = total adenine nucleotide (ATP + ADP + AMP); TASD = total adenosine nucleosides (adenosine + inosine).

rabbit heart preparation. Further investigation is needed to demonstrate the cardioprotective actions of VF 233 in in vivo models that simulate the clinical situation and use load-independent indices of left ventricular function.

The most probable mechanism of inhibition by polyhydroxybenzoic acid derivatives is destruction of free radical intermediates or metal chelation. Elford and colleagues [8] suggested that the polyhydroxybenzohydroxamic acids and their congeners may interfere with a free radical that is present during the enzymatic reaction. Two observations confirmed this hypothesis: the first series of experiment measured the degree of chelation of Fe^{3+} by mono-, di-, and trihydroxybenzahydroxamic acids. The free radical scavenging activity of these compounds increases with the number of adjacent hydroxyl groups on the phenyl ring (see Fig 1). Elford and associates [9] measured the ability of a series of hydroxy-substituted benzoic acid derivatives to destroy free radicals. There appears to be a good correlation between the ability to scavenge free radicals and the inhibition of ribonucleotide reductase [10]. Using electron paramagnetic resonance spin trap studies, a signal due to trapped hydroxyl radical has been demonstrated in the coronary effluent of reperfused hearts, whereas this signal was absent in hearts reperfused with VF 233 [21].

No significant difference in the levels of adenine nucleotide pool intermediates was observed between these two groups. This was predictable because VF 233 was administered after ischemia when ATP was equally depleted to 30% of baseline values. Correlation between ATP content and myocardial function has been controversial [22, 23] due to lack of separation between ischemic injury and reperfusion injury. We have previously shown that normal myocardium contains more ATP than it may need for basic function [16]. Correlation between ATP and function was only achieved at low but critical ATP levels when reperfusion injury was managed by specific pharmacologic interventions [16].

In summary, our findings suggest that VF 233 has myocardial protective effects likely related to inhibition of hydroxyl radical–mediated reperfusion injury. This improvement in myocardial function was not related to replenishment of myocardial high-energy phosphates. Similar results have been reported using free radical scavengers such as superoxide dismutase, catalase, and deferoxamine. Results from the present study provide further support to the notion that myocardial reperfusion injury mediated by free radicals plays a significant role in overall injury sustained by hearts undergoing ischemia and reperfusion. VF 233 may provide a basis for the development of therapeutic strategies to scavenge hydroxyl radicals during postischemic reperfusion. Observations on the beneficial effects of VF 233 are of particular interest because it is a small, low molecular weight compound that can access the intracellular compartment.

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We gratefully thank Dr Howard Elford, Molecules for Health, Inc, Richmond, VA, for supplying VF 233. We thank Laura Graham and Nancy Nixon for their technical assistance.

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Donor Heart Coronary Sinus Ostium Atresia in a Successful Cardiac Transplant

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A case of a donor heart with atresia of the coronary sinus being successfully implanted in a recipient is reported, the coronary sinus being surgically opened before implantation.

(Ann Thorac Surg 1992;53:1096–7)

Atresia of the coronary sinus ostium associated with coronary venous drainage through a left-sided superior vena cava has been described as an isolated cardiac abnormality, although in about half of previous reports it was associated with other abnormal cardiac pathology [1–4]. Most cases have been described at autopsy, although it is occasionally discovered in life [2, 3]. This report is of a heart with coronary sinus ostium atresia being successfully used for a cardiac transplant.

The donor was a previously healthy 18-year-old man who suffered brain death after a fall from a building. At explantation a small (internal diameter, 5 mm) left-sided superior vena cava was noted. Serendipitously the doctor removing the heart cut close to the atrial septum near the coronary sinus, and therefore an inspection was made of the coronary sinus. The coronary sinus was found to be closed; a probe passed from the left superior vena cava showed that the sinus was obstructed by a thin translucent membrane but that there was no opening in it. There were no openings into the left atrium. Because the recipient was in severe cardiac failure it was decided to use the heart. The donor coronary sinus was opened (Fig 1) and the entire membrane covering the ostium of the sinus was excised, the left superior vena cava then being ligated.

After reestablishment of blood supply the donor heart easily took over the work of the circulation. There was no coronary venous distention. The transplant recipient made a good recovery; however, he later died of a serious fungal infection. Up until the time of his death the donor organ functioned well with no evidence of failure or rejection.

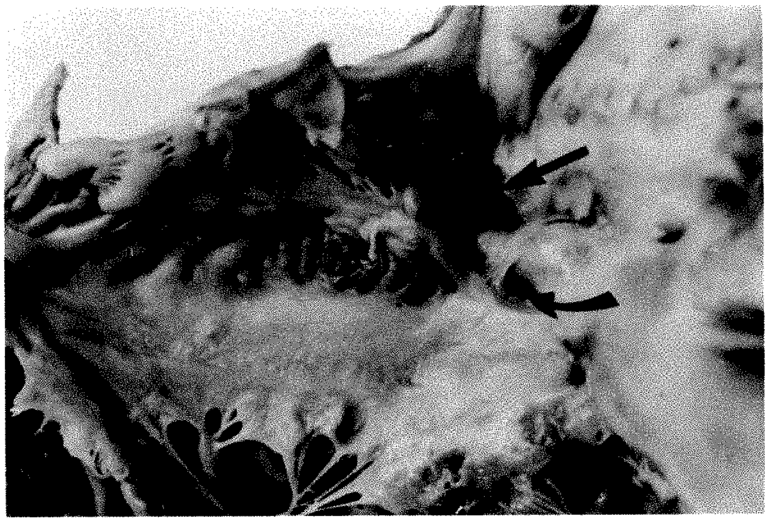

Fig 1. Appearance of surgically opened sinus ostium (straight arrow) *at autopsy. A blind ostial-like recess* (curved arrow) *lies inferior to the coronary sinus and abuts on the tricuspid valve ring.*

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Comment

Failure to recognize the role of a left-sided superior vena cava, associated with atresia of the coronary sinus ostium, as the main venous drainage channel of the heart has been implicated as a cause of death postoperatively [4]. In our case the coronary sinus was imperforate with only a thin membrane obstructing the ostium, whereas in previous reports the coronary sinus has been shown to end a variable distance from the usual ostium site [1, 4]. Because the ostium was imperforate rather than severely atretic, and the recipient's condition was critical, it was decided to use the donor heart in this case.

We would suggest that in all donor hearts where a left superior vena cava is present, patency of the coronary sinus should be checked and the presence of an imperforate coronary sinus should not be considered an absolute contraindication to the use of a donor heart. Successful transplantation of the heart may still be achieved by opening the coronary sinus.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1995 may begin the recertification process in 1993. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is May 1, 1993. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Arterial Correction of Double-Outlet Left Ventricle by Pulmonary Artery Translocation

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Double-outlet left ventricle is conventionally repaired with an intraventricular tunnel or with an extracardiac conduit when pulmonary stenosis is present. We report a 4-month-old female infant whose surgical correction of double-outlet left ventricle and subpulmonic stenosis was accomplished by pulmonary arterial translocation to the blind right ventricular infundibulum. This approach provided excellent hemodynamic repair without the use of an extracardiac conduit.

(Ann Thorac Surg 1992;53:1098–100)

Double-outlet left ventricle represents an anomalous ventriculoarterial connection with both great arteries arising wholly or in large part from the morphologic left ventricle. If pulmonary stenosis is not present, an intraventricular tunnel repair may be possible so that the right ventricle ejects into the pulmonary artery [1]. When a tunnel is not feasible, or when nonresectable subpulmonary stenosis is present, the main pulmonary orifice is closed off, the ventricular septal defect is patched, and the right ventricular outflow tract is constructed with an extracardiac conduit [2]. Infants with double-outlet left ventricle and pulmonic stenosis have been palliated with a systemic-to-pulmonary artery shunt to reduce the number of conduit changes [3]. We report a case of surgical correction in an infant with double-outlet left ventricle and subpulmonic stenosis. Our objective in translocating the pulmonary artery to the right ventricle was to avoid the use of an extracardiac conduit and its inherent morbidity.

A 4-month-old female infant was referred for management of congestive heart failure, failure to thrive, and cyanotic congenital heart disease. Preliminary evaluation demonstrated an atypical tetralogy of Fallot. She subsequently underwent cardiac catheterization, which showed double-outlet left ventricle; subpulmonary and subaortic conus; subpulmonic obstruction (50 mm Hg gradient) with mild annular hypoplasia and well-developed main and branch pulmonary arteries; bicuspid aortic valve with mild obstruction (10 mm Hg gradient); a

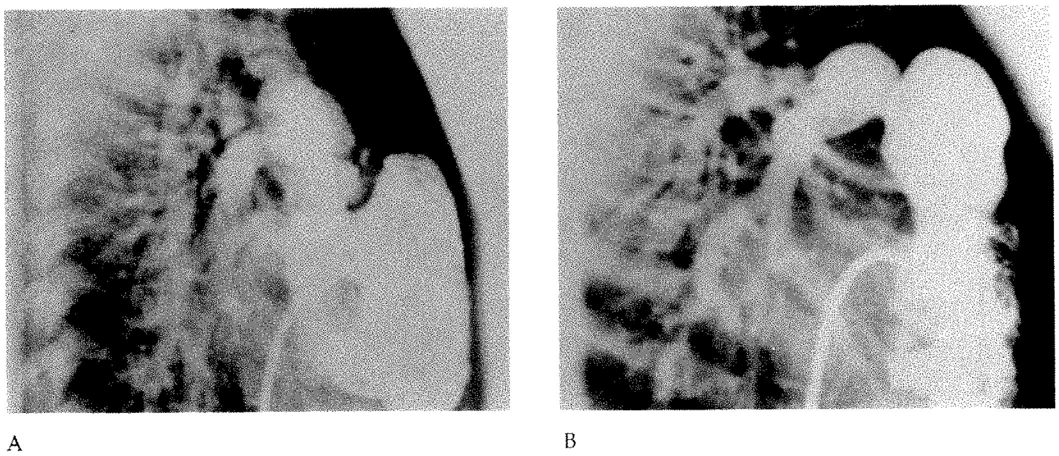

Fig 1. Left anterior oblique preoperative angiogram (A) shows a normally positioned heart with atrioventricular concordant connection and double-outlet left ventricle with subaortic ventricular septal defect. The right ventricle is anterior and its outflow tract is blind, the ventricular septal defect being the only outflow. After repair (B) ventriculoarterial concordance is established, the right ventricle is properly connected to the pulmonary artery, and the right infundibulum is widely patent.

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Table 1. Cardiac Catheterization Data

Variable	Preoperative	Postoperative
Pulmonary flow (L/min/m^2)	6.1	3.2
Systemic flow (L/min/m^2)	1.9	3.2
Pulmonary resistance (U · m^2)	6.2	2.8
Systemic resistance (U · m^2)	37	23
RV–PA gradient (mm Hg)	50	32
LV–Ao gradient (mm Hg)	15	0

Ao = aorta; LV = left ventricle; PA = pulmonary artery; RV = right ventricle.

large patent ductus arteriosus; and large atrial and ventricular septal defects (Fig 1). The right ventricular outflow tract and infundibulum ended as a blind outflow chamber. The pulmonary vascular resistance was 6.2 U · m^2, and the systemic vascular resistance was 37 U · m^2 (Table 1).

At operation the pulmonary artery and valve exited the left ventricle posteriorly and to the left of the aorta (Fig 2A). The pulmonary and aortic valves were in the same horizontal and frontal plane. There were several major coronary arteries extending across the blind infundibulum of the right ventricle. The pulmonary valve was quadricuspid, and the valve annulus measured 8 to 9 mm in diameter. A large subaortic ventricular septal defect was present.

Repair was accomplished using deep hypothermic cardiopulmonary bypass. The pulmonary artery, complete with the intact valve, was removed from the base of the left ventricle (Fig 2B). Extreme care was taken to keep both the aortic and pulmonary ring intact and to avoid the adjacent branches of the left anterior descending coronary artery. The main pulmonary artery and its branches were dissected out to each hilum, so that the main pulmonary artery could swing rightward in front of the aorta to join the right ventricular outflow tract. The residual defect in the left ventricle was directly sutured both from within the ventricle and on the epicardial surface. The atrial septal defect was sutured. The ventricular septal defect was closed through a right infundibulotomy. The main pulmonary artery with its valve was anastomosed to the base of the infundibulotomy (Fig 2C). Right ventricular closure was completed with a hood of autologous pericardium (Fig 2D). Cardiopulmonary bypass was weaned while dopamine was infused into the baby at 3 μg/kg/min.

The postoperative course was complicated by mild right ventricular failure and transient focal seizures 2½ days after operation. She was extubated on the fourth postoperative day. Echocardiographic evaluation indicated moderate right ventricular outflow obstruction and elevated right ventricular pressure. She was discharged on the 12th postoperative day receiving digoxin and diuretics. A heart catheterization was performed on the 14th postoperative day. The study revealed an excellent anatomic repair (see Fig 1) characterized by a mildly to moderately hypoplastic pulmonary annulus (32 mm Hg gradient), no left ventricular outflow tract gradient, and a tiny residual muscular ventricular septal defect (Tables 1 and 2).

Comment

Double-outlet left ventricle is a rare malformation that has been reported with some regularity since 1967, when Sakakibara and colleagues [1] reported the first successful intraventricular repair. The assignment of both great

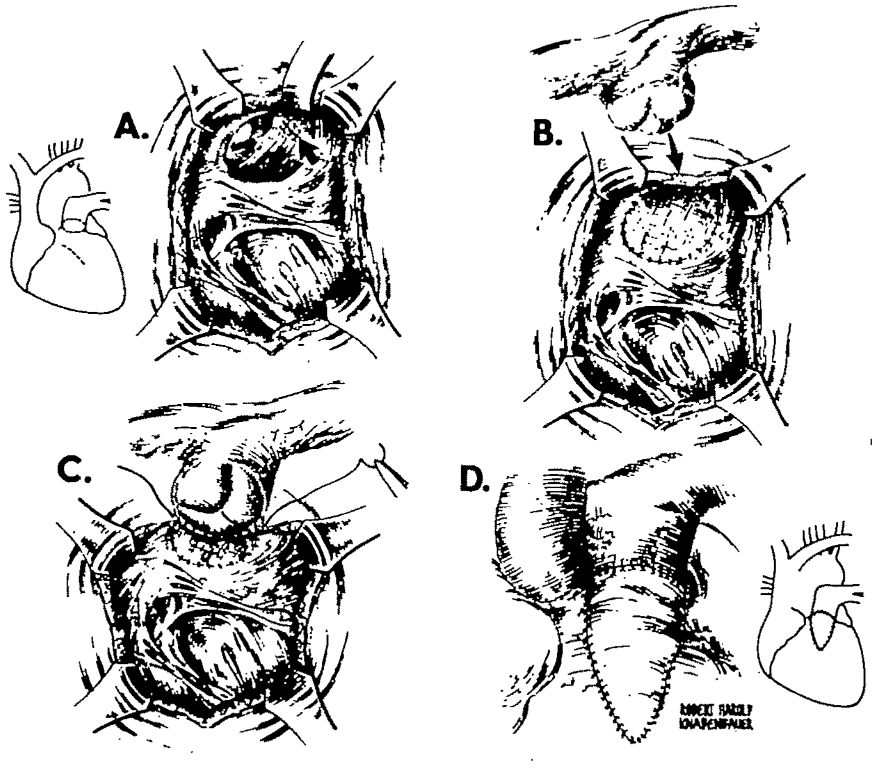

Fig 2. Surgical technique for pulmonary artery translocation from left to right ventricle: (A) The aorta is to the right of the pulmonary artery and in the same frontal plane. The right ventricle is opened by a vertical incision. The subpulmonary area is closed through the ventricular septal defect. (B) The main pulmonary artery is dissected carefully to keep the valve intact and to avoid damage to the adjacent left anterior descending coronary artery. The pulmonary outflow tract is now closed from the outside and the ventricular septal defect is patched. (C) The pulmonary valve ring is now inserted in the superior right ventricular wall where the pulmonary artery would normally arise. (D) A patch of pericardium is now cut to an approximately semilunar shape and sutured into place to complete the anterior half of the anastomosis. The pulmonary artery now arises from the right ventricle in the same position as in ventriculoarterial concordance.

Table 2. Oxygen Saturations and Blood Pressures

	Preoperative		Postoperative	
Location	O_2 Saturation	Pressure (mm Hg)	O_2 Saturation	Pressure (mm Hg)
Superior vena cava	49%	NA	62%	NA
Inferior vena cava	NA	NA	64%	NA
Right atrium	63%	6	63%	9
Right ventricle	NA	115/8	63%	62/10
Pulmonary artery	78%	65/30 (44)[a]	63%	30/8 (15)
Left atrium	92%	6	NA	NA
Left ventricle	NA	115/5	NA	100/6
Aorta	82%	100/40 (70)	92%	100/55 (75)

[a] Numbers in parentheses are mean pressure.

NA = not available.

arteries to the left ventricle follows the 50% rule, and the results by echocardiographic and angiographic images can be different from the appearance in the autopsied heart. Paul and colleagues [4] in 1970 established the existence of this entity by describing a specimen with double-outlet left ventricle and intact ventricular septum.

Intraventricular repair may be accomplished in double-outlet left ventricle and subpulmonary ventricular septal defect without subpulmonic stenosis by intraventricular channeling of the ventricular septal defect [1]. Double-outlet left ventricle with subaortic ventricular septal defect without pulmonary stenosis may be repaired with a boomerang-shaped patch, as originally described by McGoon [5] for intraventricular correction of transposition of the great arteries. Intraventricular repair may sometimes be accomplished in the presence of pulmonary stenosis, when a subpulmonary fibromuscular ring can be satisfactorily excised. Usually, however, the right ventricular outflow tract has to be constructed using an external valved conduit [6].

An extracardiac conduit repair initially provides a satisfactory right ventricular to pulmonary pathway, but one that cannot grow and is subject to late conduit obstruction. Thus, reoperation is anticipated in this form of repair. The hospital mortality after correction of double-outlet left ventricle and atrioventricular concordance with a valved extracardiac conduit has been 28% (70% confidence limits, 16% to 43%) in the combined University of Alabama in Birmingham and Green Lane Hospital series [3].

Ventricular septal defect closure in double-outlet left ventricle does not require construction of a pathway for left ventricular to aortic blood flow (as in double-outlet right ventricle). Outflow from the right ventricle to the pulmonary arteries needs to be constructed, and theoretically, the pulmonary artery trunk and valve might be readily detached from the left ventricle and reimplanted into the right ventricle. End-to-end anastomosis between the dislocated pulmonary valve and the right atrial appendage was reported by Kreutzer and associates [7] in 1973 to accomplish atriopulmonary connection for correction of tricuspid atresia. The same concept has been applied by Ishikawa and colleagues [8] to infants with tricuspid atresia. A direct anastomosis between the mobilized pulmonary artery and the right atrial appendage allows adequate growth of the pulmonary valve. Furthermore, the pressure gradients present at the end of the procedure disappeared at cardiac catheterization 4 to 7 years postoperatively.

Translocation of the pulmonary artery to correct double-outlet left ventricle is feasible in infants as indicated in our report. Only moderate obstruction across the pulmonary valve was present early in the postoperative period, and perhaps this will decrease further with time. Pulmonary arterial growth is theoretically more likely in the setting of a widely pulsatile flow [9] than in the continuous-flow physiology of an atriopulmonary anastomosis. In the event of a persistent right ventricular outflow tract obstruction at follow-up, the patient may be a candidate for balloon valvuloplasty rather than obligatory reoperation.

We acknowledge the assistance of V. Reddy, MD, in preoperative and postoperative care and evaluation.

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Mediastinoscopic Injury to the Bronchus: Use of In-Continuity Bronchial Flap Repair

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There is little written in the literature regarding the management of major bronchial disruptions occurring during mediastinoscopy. This report illustrates the use of an in-continuity flap bronchoplasty of middle lobe bronchial tissue to repair such an iatrogenic intermediate bronchus injury.

(Ann Thorac Surg 1992;53:1101–3)

Iatrogenic complications of mediastinoscopy are relatively rare, however, urgent operation may be required when a major vascular or tracheobronchial injury occurs [1]. Description of the management of iatrogenic trauma resulting from mediastinoscopic biopsy is superficially addressed in the literature, although such injuries have been reported to occur in up to 2% of patients undergoing this diagnostic procedure [2]. We illustrate the in-continuity bronchial flap repair of an intermediate bronchus injury occurring during the biopsy of an extensive mediastinal and hilar fibrosing process.

An otherwise healthy 44-year-old man complained of recurrent fevers (to 39.5°C), exertional dyspnea, pleuritic chest pain, and a nonproductive cough for 10 days' duration. But for a history of smoking (10 pack-years), the patient's past social and medical history were unremarkable. He did, however, admit to having a similar respiratory symptom complex 7 months earlier. Chest roentgenography at that time revealed a right lower lobe pulmonary infiltrate. He was empirically treated with oral ampicillin and erythromycin. Symptomatic recovery was achieved over the ensuing 3 weeks.

A chest roentgenogram obtained during the present illness revealed new right hilar prominence without residual pulmonary infiltrates. Computed tomography demonstrated a mass in the right hilum encasing the bronchus intermedius and right paratracheal lymphadenopathy (Fig 1). Physical examination was notable only for auscultation of right sided posterobasilar coarse rales. There was no palpable adenopathy. Laboratory analyses were normal. A skin test anergy panel demonstrated a lack of reactivity to tuberculin and positive reactions to dermatophytes and mumps.

Fiberoptic bronchoscopy revealed mild mucosal edema and minimal narrowing of all right-sided lobar and segmental bronchi. No endobronchial lesions were seen. Bronchial brushings and washings sent for cytologic and microbiologic study were nondiagnostic. Transcarinal and right-sided transbronchial needle biopsies were also unrevealing. Thoracic surgery consultation was obtained for mediastinoscopic biopsy to diagnose this process.

Standard transcervical mediastinoscopy was performed after induction of anesthesia [1]. The upper pretracheal tissue plane was easily developed with gentle finger dissection. No masses were palpated. The mediastinoscope could be passed easily to just above the carina. Frozen section analysis of the right-sided low paratracheal lymph nodes demonstrated nodal hyperplasia only. Beyond the carina, a dense fibrotic process about the right main bronchus distorted local tissue planes. Frozen section analysis of multiple biopsy specimens from this area revealed reactive desmoplasia only. Persistent sampling in this area was ultimately met with a rush of air from the area of biopsy through the mediastinoscope (Fig 2). The anesthesiologist immediately noted an inability to ventilate the patient. Ventilatory volume loss was controlled by removing the mediastinoscope and packing the wound with a dry gauze sponge. A double-lumen endotracheal tube was inserted to obtain selective ventilation of the left lung. The patient was then placed in a lateral position in preparation for right lateral thoracotomy. The bronchial injury was approached through the right fifth intercostal space. Diffuse peribronchial fibrosis made dissection of the pulmonary hilum quite tedious. A 1.5-cm (length) ×

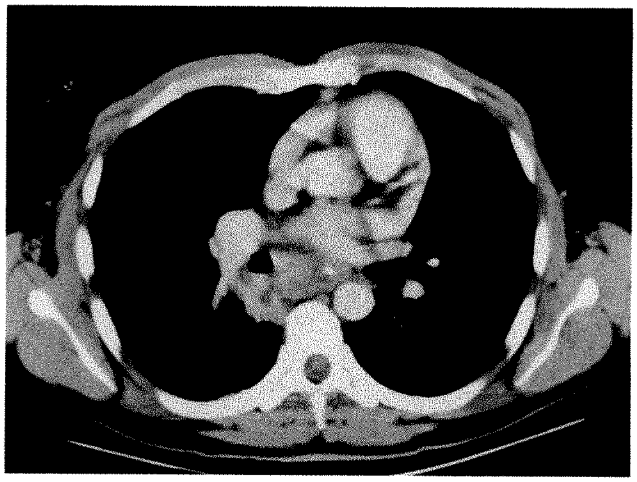

Fig 1. Computed tomographic scan of the chest demonstrating the peribronchial process encasing the right main bronchus.

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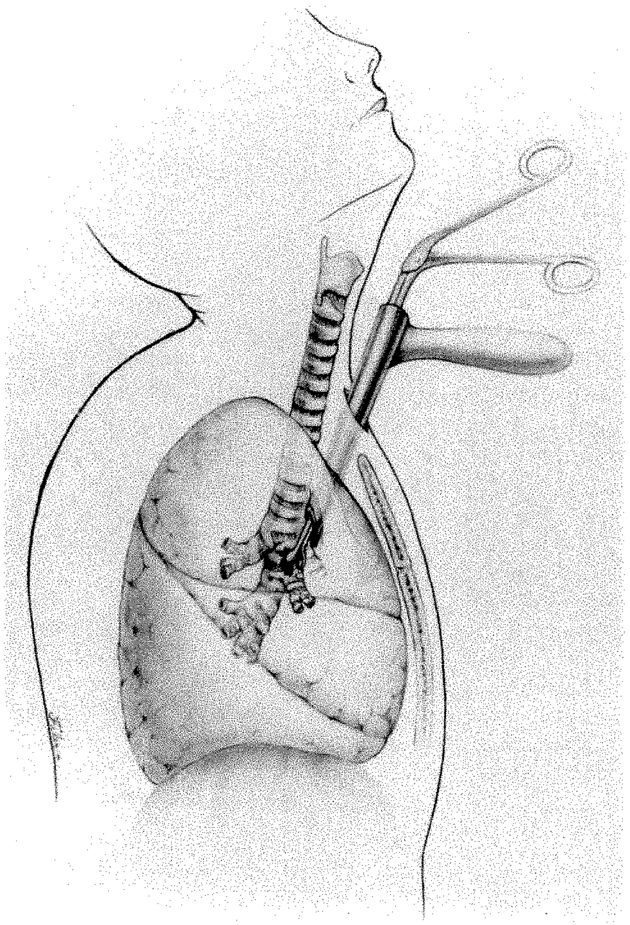

Fig 2. Illustration of the lateral aspect of the pretracheal space and the mediastinoscope's position during the peribronchial biopsy.

1.0-cm (width) defect in the anterior aspect of the bronchus intermedius, beginning 2 mm distal to the base of the right upper lobe bronchus, was found. The middle lobe bronchus was intact. Primary repair was impossible due to the size and irregular margins of the bronchial defect. Bronchoplasty repair was considered; however, the underlining hilar fibrosis prevented adequate mobilization of the bronchus for this reconstruction.

The middle lobe bronchus appeared to be ideally suited for bronchial flap repair of this extensive intermediate bronchus injury. Middle lobectomy was required. Preservation of the entire middle lobe bronchus beyond the segmental bifurcation was performed during the course of lobectomy. An incision was then made along the anterior cartilaginous surface of the middle lobe bronchus and extended through the distal extent of the intermediate bronchus injury (Fig 3). The irregular edges of the bronchial defect were debrided, and the spatulated middle lobe bronchus was then folded over the defect to begin the flap patch bronchoplasty. The open edges of the middle lobe bronchus were approximated to the margins of the intermediate bronchial defect using 4-0 interrupted polypropylene suture [3]. The bronchial repair was found to be airtight when tested with reexpansion of the right lung. The pericardial fat pad was then mobilized over the flap bronchoplasty to buttress the repair.

There was no postoperative air leak from the tube thoracostomy, and chest roentgenography confirmed total expansion of the right lung. The final pathologic analysis of the mediastinal tissue obtained at operation revealed necrotizing granulomata consistent with histoplasma granulomatous mediastinitis. The patient's recovery was uneventful. He is being treated with a 6-week course of fluconazole.

Comment

Little information regarding the management of mediastinoscopic airway injuries is available in the literature. In a series of more than 2,000 mediastinoscopies, Puhakka [2] reported three tracheal disruptions, which he successfully managed with transmediastinoscopic tamponade of the rent in the airway with absorbable cellulose gauze (Surgi-

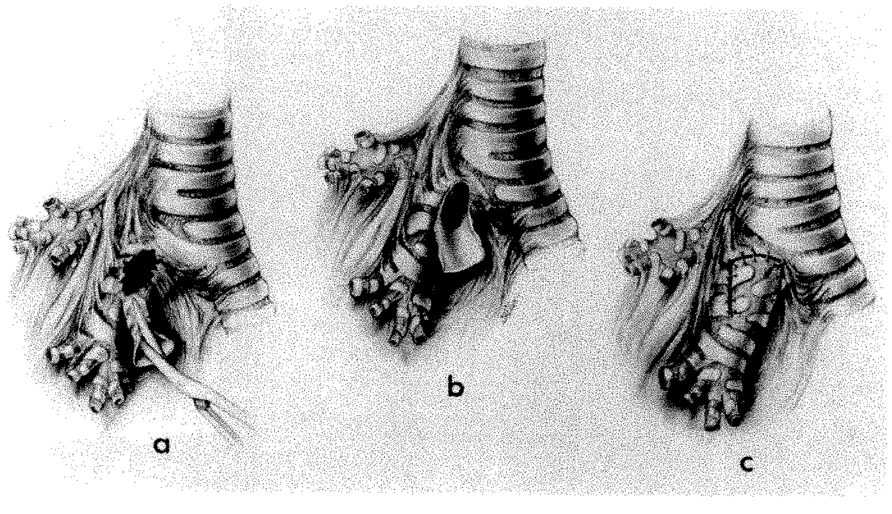

Fig 3. (a) Illustration of the extent and location of the intermediate bronchus injury and its relationship to the middle lobe bronchus (middle lobe parenchyma excluded). (b) Line of incision through the middle lobe bronchus used to create the spatulated hood for the intermediate bronchus repair. (c) Middle lobe bronchial flap sutured in place over the debrided edges of the intermediate bronchial injury.

cal, Johnson & Johnson, New Brunswick, NJ). Although this management may be successful for small bronchial disruptions, injuries similar to that described here will usually require open thoracotomy for repair [4–6]. Although injury debridement and primary repair is the first consideration, local resection with an end-to-end bronchial anastomosis may be necessary for more extensive injuries. Both of these approaches require that adequate normal bronchial tissue be mobilized without tension to accomplish the repair [4–6]. Other repair options available include onlay of a pedicled pericardial or intercostal muscle flap over the injury [7]; however, repair dehiscence and delayed bronchial stricture may be more common with these techniques. We illustrate a method of bronchial flap reconstruction that may be considered for extensive iatrogenic or primary traumatic bronchial injuries [5–7]. This repair may be desirable for such serious injuries in selected circumstances.

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Aorto–Pulmonary Artery Fistula: An Unusual Complication of Ascending Aortic Aneurysm

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We report an unusual outcome of an ascending aorta aneurysm ruptured into the main pulmonary trunk. After successful emergency repair, an acute respiratory distress syndrome developed perioperatively and complicated the postoperative period. The patient could not be weaned from mechanical ventilation for a long time. The patient was discharged on the 62nd day of admission in good condition.

(Ann Thorac Surg 1992;53:1104–6)

A 52-year-old male patient was admitted to the hospital with severe dyspnea and pretibial edema. In the patient's history, dyspnea had existed for a year, sometimes becoming exacerbated. With an acute worsening in his condition he had been admitted to a local hospital. As a result, ascending aorta aneurysm diagnosis was confirmed by computed tomography (Fig 1). Then the patient was sent to our hospital and taken to the intensive care unit with grade IV symptoms. The patient was orthopneic with severe bilateral pretibial edema. His systemic arterial pressure was 100/60 mm Hg, and the pulse was at a rate of 100 beats/min with regular rhythm. On auscultation, the lungs were noisy with rhonchi, wheezes, and crepitant rales. The electrocardiogram was normal. Abnormalities in the laboratory test results were as follows: white blood cells, 18.2×10^9/L (18,200/μL); hematocrit, 0.28; hemoglobin level, 90 g/L; nonprotein nitrogen, 162 mg/dL; prothrombin time, 15 seconds; prothrombin activity, 45% of normal; activated partial thromboplastin time, 26 seconds; and oxygen tension, 49 mm Hg on oxygen adminstered by mask. Chest roentgenogram showed diffuse pulmonary infiltrates with enormous enlargement of the ascending aorta (Fig 2A). When these results were obtained, the condition of the patient was worsening and onset of rupture was suspected. Decision for prompt operation was made.

After the routine anesthesic procedure was completed, preparations for femoral cannulation and a median sternotomy incision were made. After pericardiotomy, an approximately 20 × 20-cm ascending aortic aneurysm extending to the origin of the innominate artery was seen. There was no rupture or false aneurysm formation. A systolodiastolic thrill was palpated on the aorta, and a fistula formation was suspected. Cardiopulmonary bypass was established with femoral arterial cannulation and a single venous cannula placed through the right atrial appendage. The patient was cooled to 24°C with partial bypass, and an aortic cross-clamp was placed just proximal to the innominate artery. An aortotomy incision was made and blood sucked out for visual evaluation. Approximately 1,000 mL of crystalloid cardioplegic solution was delivered through the coronary artery ostia. There was no dissection but a cut-edge, round orifice of the aortopulmonary artery fistula 2 cm in diameter was seen (Fig 3). The defect in the pulmonary artery wall was repaired with three separate Teflon-pledgeted polypropylene sutures. On visual evaluation, the aortic valve and ring were normal. Then a 30-mm low-porosity woven Dacron graft was interposed in the supracoronary position. Aortic cross-clamp time was 35 minutes. After rewarming, the patient was weaned from cardiopulmonary bypass without any problem. No inotropic or mechanical support was needed.

Acute respiratory distress syndrome that developed perioperatively complicated the postoperative course, and the patient could not be weaned from mechanical ventilation until the 45th postoperative day (Fig 2B).

After complete recovery, a control angiography was performed and showed no abnormality (Fig 4). The patient was discharged on the 62nd day after operation in good condition. Two months later, when he came for the

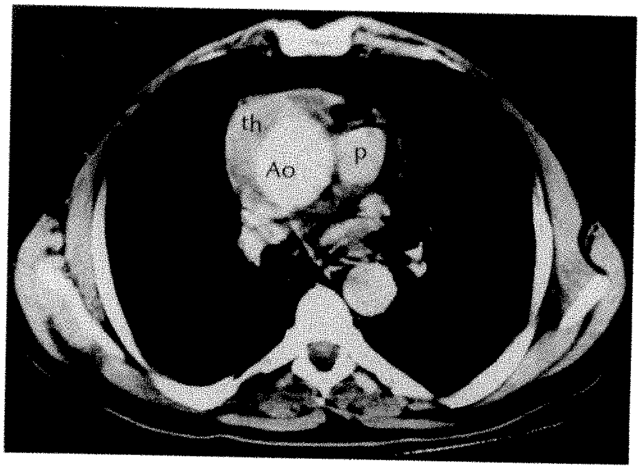

Fig 1. Ascending aortic aneurysm with intraluminal thrombus is seen in this computed tomographic plane. (Ao = *aorta;* p = *pulmonary artery;* th = *Intraluminal thrombus.)*

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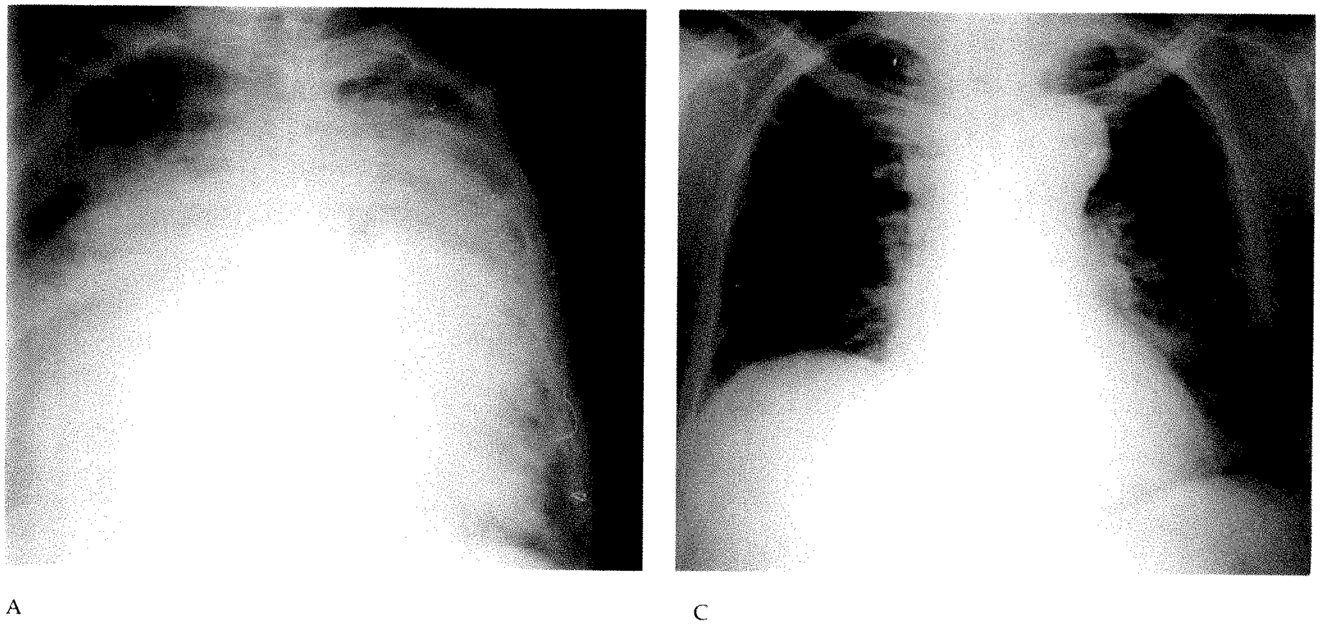

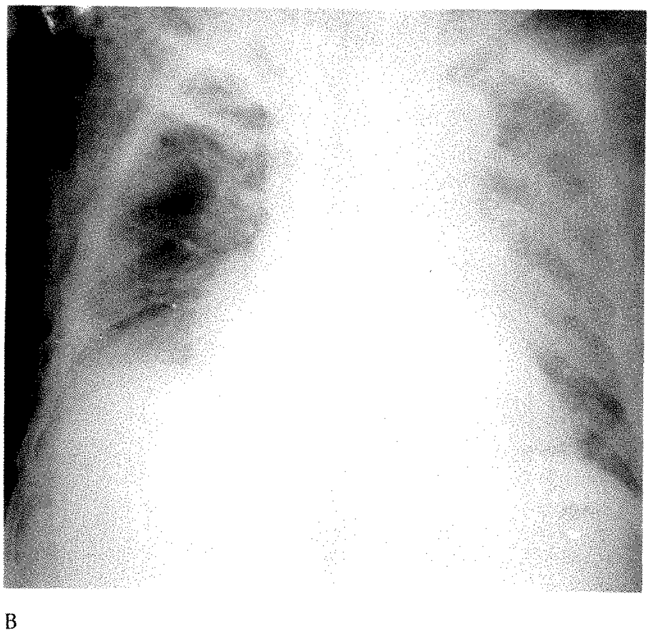

Fig 2. Chest roentgenograms before (A), 4 days (B), and 4 months (C) after the operation.

first follow-up check, he was fine without any symptoms, and the chest roentgenogram (Fig 2C) showed no abnormalities.

Comment

Ruptured ascending aortic aneurysms have a poor prognosis, and death occurs in a great majority of patients. In the case we presented, aneurysmal penetration to the pulmonary artery resulted in an aortopulmonary artery fistula formation followed by congestive failure and respiratory distress syndrome.

Among the previously reported complications, aneurysmal penetrations that resulted in fistula formation to the caval vein [1, 2], to the left renal vein [3], and to the right atrium [4, 5] have been mentioned. Even cases with aortopulmonary artery fistulizations have been reported [6], but they are of traumatic nature, and penetrating chest injuries are responsible for such cases. Our patient had no history of penetrating chest trauma, and the aneurysm was not a dissecting one. In Dr Crawford's textbook of *Diseases of the Aorta* [7], a transverse aortic arch aneurysm penetrating to left pulmonary artery is reported. This case is similar to ours in its nature and congestive symptoms, but the location is different.

In our patient's history an acute worsening of his condition 1 week previously to the operation might be considered the time that ultimate fistulization occurred. Henze and associates [5] reported symptoms of right ventricular failure and intractable ascitis due to increased right ventricular volume work after the rupture of a dissecting aortic aneurysm into the right atrium. Ingram and colleagues [8] reported progressive heart failure secondary to a high output state due to arteriovenous hemodialysis fistulas, suggesting that volume overload from the high output state may depress ventricular function.

Regarding the perioperative respiratory distress syndrome, several mechanisms might be considered. Persistence of deteriorated pulmonary function despite closure of the fistula suggested that the patient's respiratory distress was not caused by pulmonary congestion alone and there had to be some other mechanisms. Respiratory distress syndrome may be caused by high-pressure flow through the aorta into the pulmonary vascular bed, which is unaccustomed to such high-pressure flows. This may lead to pulmonary edema and could be destructive to

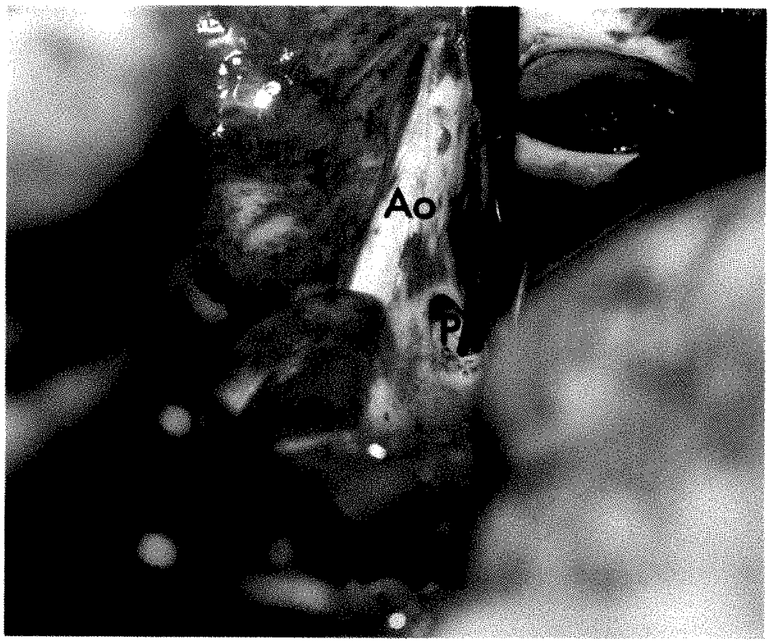

*Fig 3. Clamp passing across the aortopulmonary fistula. (*Ao = *inner layer of aneurysmal aorta;* p = *lumen of the main pulmonary artery seen from the fistula window.)*

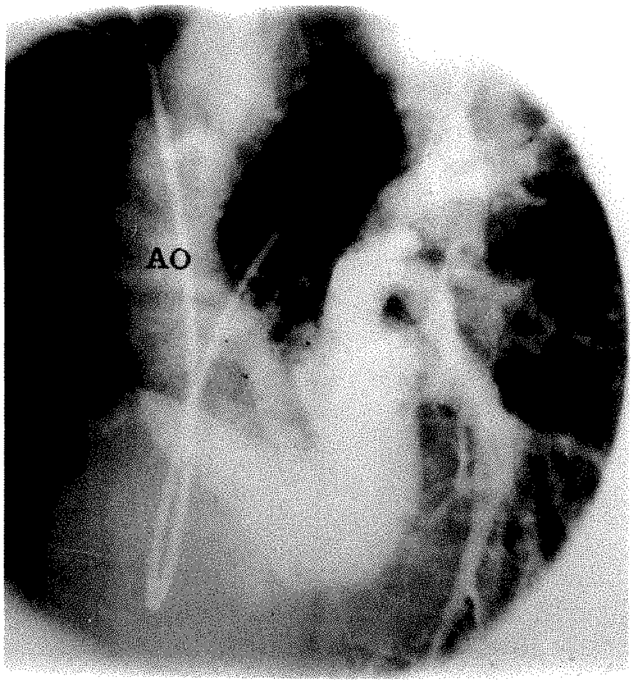

*Fig 4. Control angiogram (late aortic phase of right ventricular injection) before discharging. Contrast material is injected into right ventricle and ascending aorta is visualized in the late phase. (*AO = *aorta.)*

structural components. Even the harmful effects of cardiopulmonary bypass on lungs might have contributed to this process. This point needs further evaluation.

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Aortico–Right Ventricular Tunnel

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We report successful closure of an aortico–right ventricular tunnel in a 3-month-old infant with heart failure. One-year follow-up shows the child to be developing normally.

(Ann Thorac Surg 1992;53:1107–9)

Whereas aortico–left ventricular tunnel is an unusual but well-recognized congenital anomaly, aortico–right ventricular tunnel is exceptionally rare [1]. We describe a patient with aortico–right ventricular tunnel who was seen in early infancy and was successfully treated by surgical closure.

The male infant was the second of twins born at 37 weeks' gestation (weight, 2.9 kg). He failed to thrive in comparison with his sibling and had development of heart failure at 11 weeks. Systolic and diastolic murmurs were noted at the left sternal edge together with bounding carotid, brachial, and femoral pulses. The first clinical diagnosis was of patent ductus arteriosus, but there was little improvement on medical management and he was referred to the Oxford Heart Centre for further investigation.

Plain chest roentgenography showed cardiac enlargement. Two-dimensional echocardiography demonstrated a free communication between the aorta above the right aortic sinus and the right ventricular outflow tract (Fig 1). The right coronary artery could not be clearly separately identified. The aortic valve had three cusps and was mildly regurgitant. The left ventricle was volume overloaded and there was mild mitral regurgitation. The differential diagnosis at this stage was a right coronary artery fistula or aortico–right ventricular tunnel. Cardiac catheterization confirmed the connection between the aorta and the right ventricular outflow tract but could not clearly differentiate between the suspected lesions.

At operation, the heart was enlarged with distention of the right ventricle and main pulmonary artery. Externally there was an out-pouching of the aorta on its right anterior side. This was continuous with a membranous structure beneath the aorta, which in turn continued into a bulge of the right ventricular outflow tract. There was a pronounced systolic and diastolic thrill in this structure and in the pulmonary outflow tract.

Cardiopulmonary bypass was established with an ascending aortic arterial cannula and a single venous cannula in the right atrium. Systemic cooling to 20°C was undertaken to ensure myocardial protection. It was not considered desirable to infuse cardioplegia directly the coronary arteries, but with external compression of the tunnel 50 mL of St. Thomas' solution were infused into the cross-clamped aortic root. A longitudinal aortotomy was used to expose the defect and the adjacent coronary ostia.

The aortic annulus and valve were normally formed. At the upper margin of the right sinus of Valsalva there was a wide opening in the aorta and a tunnel 0.8 cm in length which entered the infundibulum of the right ventricle (Fig 2). This corresponded to the out-pouching of the aorta seen externally (proximal chamber of the tunnel). The endothelium of the tunnel resembled that of the aorta. The right coronary ostium was situated immediately to the right of the tunnel (surgeon's view), and the left coronary ostium was normally situated in the left sinus of Valsalva. Both coronary arteries were normal in distribution. Passage of a probe through to the right ventricular outflow tract confirmed the diagnosis of aortico–right ventricular tunnel.

The defect was closed with a composite patch of Gore-Tex (W.L. Gore & Assoc, Naperville, IL) covered with autogenous pericardium on the aortic aspect (Fig 3). This measured 0.8 cm in diameter and was sewn into place with continuous 5-0 Prolene (Ethicon, Somerville, NJ), care being taken to avoid narrowing or distortion of the right coronary ostium and right coronary cusp. Cardiopulmonary bypass was discontinued without difficulty, and the child made an uneventful recovery.

Postoperatively, there was a dramatic improvement in feeding and weight gain. At follow-up 12 months later (aged 15 months) the infant had no abnormal cardiovascular signs and was thriving without medication. Two-dimensional echocardiography and color flow Doppler echocardiography showed no cardiovascular abnormality. Specifically, there was no residual aortic regurgitation.

Comment

Our patient's heart has many similarities but some differences from that described by Bharati and associates [1]. Bharati and associates' postmortem heart came from a twin whose sibling was normal. This infant had a rapidly deteriorating condition and died 6 hours after birth. The tunnel arose from the right sinus of Valsalva and had identical morphology, apart from the coronary anatomy. The right coronary ostium arose from the distal part of the tunnel and not from the sinus of Valsalva. Also, the left circumflex coronary artery arose from the distal part of the canal separate from the origin of the right coronary artery.

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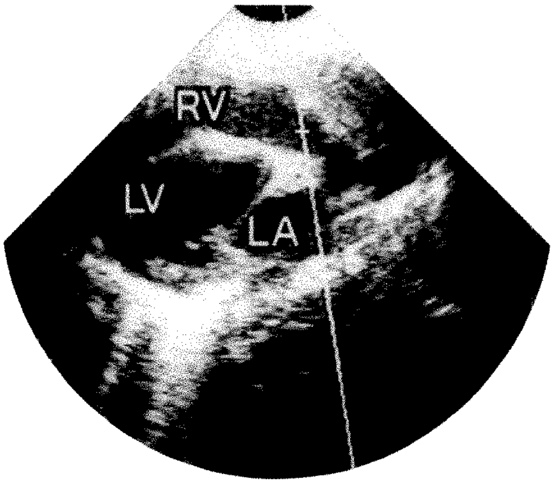

Fig 1. Parasternal long-axis ultrasound scan showing the full length of the tunnel that enters into the infundibulum of the right ventricle (RV). The left coronary sinus and aortic valve are structurally normal. (LA = *left atrium;* LV = *left ventricle.*)

Bharati and associates noted that the right sinus of Valsalva was abnormal in their specimen. The supravalvar ridge related to the sinus was situated low so that the right sinus of Valsalva was shallower than the other two aortic sinuses. There was hypertrophy and enlargement of the right ventricle, and internally the tunnel entered as an aneurysmal formation above the parietal band. There was an atrial septal defect of the fossa ovalis type.

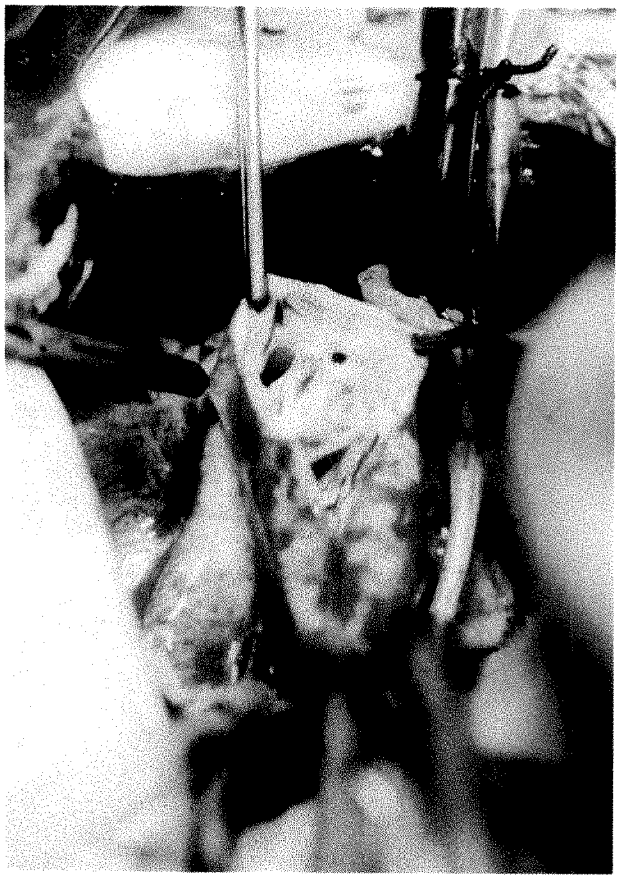

Fig 2. Operative photograph showing the opening of the tunnel from an abnormal right coronary sinus. The normal right coronary ostium is seen to the right of the tunnel.

The pathogenesis of aortico–right ventricular tunnel is unknown, although the defect resembles aortico–left ventricular tunnel. In the latter the opening in the aorta is situated above the left sinus of Valsalva and the canal tunnels its way through the ventricular septum to enter into the left ventricle [2, 3]. Fistulation between the aorta and right ventricle during embryogenesis leads to altered hemodynamics with left to right shunt occurring throughout fetal life and after birth. This produces pressure and volume hypertrophy of the right ventricle, a finding noted in our surgical case. Aortico–left ventricular tunnel mimics torrential aortic regurgitation.

Suggestions for pathogenesis of aortico–left ventricular tunnel include abnormal formation of the supravalvular ridge [1, 4], defective incorporation of the distal end of the bulbus cordis [5], primary separation of the aortic ring from the fibrous skeleton of the heart [6], retrograde dissection related to Marfan's syndrome [7], and accessory or anomalous coronary artery formation communicating with myocardial sinusoids [3]. Cardiac lesions associated with aortico–left ventricular tunnel include bicuspid aortic valve, aortic stenosis, right ventricular outflow obstruction, valvular pulmonary stenosis, patent ductus arteriosus, absent right coronary artery, sinus of Valsalva aneurysm, and aneurysm of the interventricular septum [2].

One might expect the clinical syndrome in aortico–right ventricular tunnel to be similar to the left-sided anomaly. The defect is more common in males and usually is seen early in infancy with a to and fro murmur, bounding peripheral pulses, cardiomegaly, and dilatation of the aortic root. The majority of patients have congestive heart failure, and a precordial diastolic thrill may be palpable. These findings may also occur with large coronary artery fistulas, a diagnosis that was originally favored in our patient in view of the extreme rarity of aortico–right ventricular tunnel.

In the case of aortico–left ventricular tunnel, diagnosis can usually be obtained by two-dimensional echocardiography and color-flow Doppler imaging [8]. In our patient, the aortogram did not contribute substantially because contrast medium was rapidly disseminated from the aorta and it was not possible to differentiate between a tunnel or a very proximal right coronary fistula.

Surgical closure has been advised for all patients with aortico–left ventricular tunnel, and this must apply to the right-sided derivative [2]. Nevertheless, Serino and colleagues [5] have demonstrated residual aortic regurgitation after surgical closure of aortico–left ventricular tunnel, which may require reoperation and eventual valve replacement. They consider that weakness persists in the aortic root after closure and that the aortic valve is poorly supported in the involved coronary sinus. Closure of the

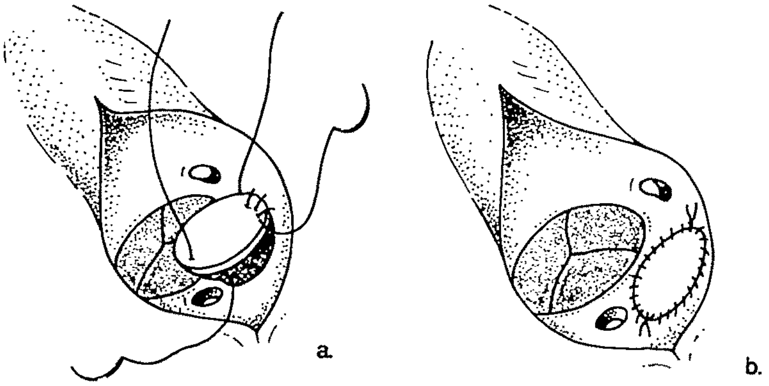

Fig 3. Composite patch closure of the aortic end of the aortico–right ventricular tunnel. (a) A pericardium-covered Gore-Tex patch is sewn over the aortic aspect of the tunnel by continuous suture. (b) The tunnel is securely closed without distortion of the right coronary cusp or coronary arteries.

defect must be undertaken without distorting the aortic cusps and should reduce the size of the aneurysmal sinus and aortic root.

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Cryopreserved Allograft Repair of Aortic Hypoplasia and Interrupted Aortic Arch

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Mortality for interruption of the aortic arch approaches 100% within the first year of life if untreated. Prostaglandin E_1 can stabilize the patient's condition in anticipation of surgical palliation, but total repair is required for long-term survival. Successful complete repair of type B interrupted aortic arch, hypoplasia of the left ventricular outflow tract, and ventricular septal defect was possible using a cryopreserved allograft in a child who previously had undergone unusual palliation.

(Ann Thorac Surg 1992;53:1110–3)

Interruption of the aortic arch comprises 1.4% of all congenital cardiac lesions [1]. If the anomaly is untreated, mortality approaches 100% within the first year of life [2, 3]. Intravenous prostaglandin E_1 is crucial in maintaining ductal patency, thereby avoiding or reversing metabolic acidosis in the newborn period. To support extended survival, surgical intervention is required. Substantial operative mortality is associated with palliation and with complete repair in the neonate. If palliation is chosen, it usually consists of reconstruction of the interrupted aortic arch and pulmonary artery (PA) banding. Innovative surgical repair with a cryopreserved aortic valve allograft was accomplished in a child who had previously undergone an unusual method of palliation secondary to his small size and associated lesions.

A 1,500-g premature male infant was born with hypoplasia of the aortic valve annulus, root, and ascending aorta; interrupted aortic arch; aberrant right subclavian artery; patent ductus arteriosus; and a large ventricular septal defect (VSD). Because of his small size, the neonate underwent placement of a synthetic graft conduit from the main PA to the descending thoracic aorta and banding of the distal main PA.

At 2 years of age, total surgical repair was attempted. Intraoperatively, conventional complete repair was impossible due to extreme hypoplasia of the left ventricular outflow tract. Because cardiac transplantation was deemed the only other alternative, the child was referred for placement of an aortic valve allograft to establish adequate left ventricular outflow and aortic arch continuity.

Preoperatively, the child was mildly cyanotic with minimal clubbing and normal vital signs. Auscultation revealed a systolic murmur along the left sternal border. Laboratory values and further physical examination were within normal limits.

In the operating room, the chest was reopened and dense adhesions were dissected. After systemic heparinization, bicaval and dual arterial cannulation was accomplished and cardiopulmonary bypass with immediate cooling was instituted. An apical left ventricular vent was inserted and a cardioplegia administration catheter was placed into the proximal aorta. The synthetic PA to descending aorta graft was ligated and divided proximal to the cannula (Fig 1A).

The main PA was resected distal to the band and proximal to the synthetic graft anastomosis. The stenotic origin of the right PA was then incised longitudinally. The transected ends of the main PA were anastomosed, enlarging the right PA orifice (Fig 1B).

A cryopreserved aortic valve allograft with 14 mm internal diameter was chosen to create a new left ventricular outflow tract. The allograft left carotid and subclavian arteries were trimmed flush with the conduit and sutured closed. End-to-end anastomosis was performed between the distal allograft conduit and native descending thoracic aorta. The aorta was cross-clamped, and cold sanguineous cardioplegia was administered. A right ventriculotomy was performed. The ascending aorta was carefully transected immediately above the valve proximal to the coronary ostia and closed as a blind pouch. The small bicuspid aortic valve and subvalvar aortic membrane were resected. The annulus and subvalvar area were opened into the VSD (Fig 1C).

The interventricular septum was augmented with a polytetrafluoroethylene patch sutured anteriorly, inferiorly, and posteriorly. Running suture was used to anastomose the proximal aortic valve allograft to the patient's aortic annular region posteriorly. The superior aspect of the VSD patch was sutured to the anterior muscular rim of the allograft (Fig 2A).

The open brachiocephalic ostium remaining in the allograft conduit was extended proximally with a longitudinal incision. Tourniquets were tightened around the native arch vessels. A 15-mm longitudinal aortotomy was

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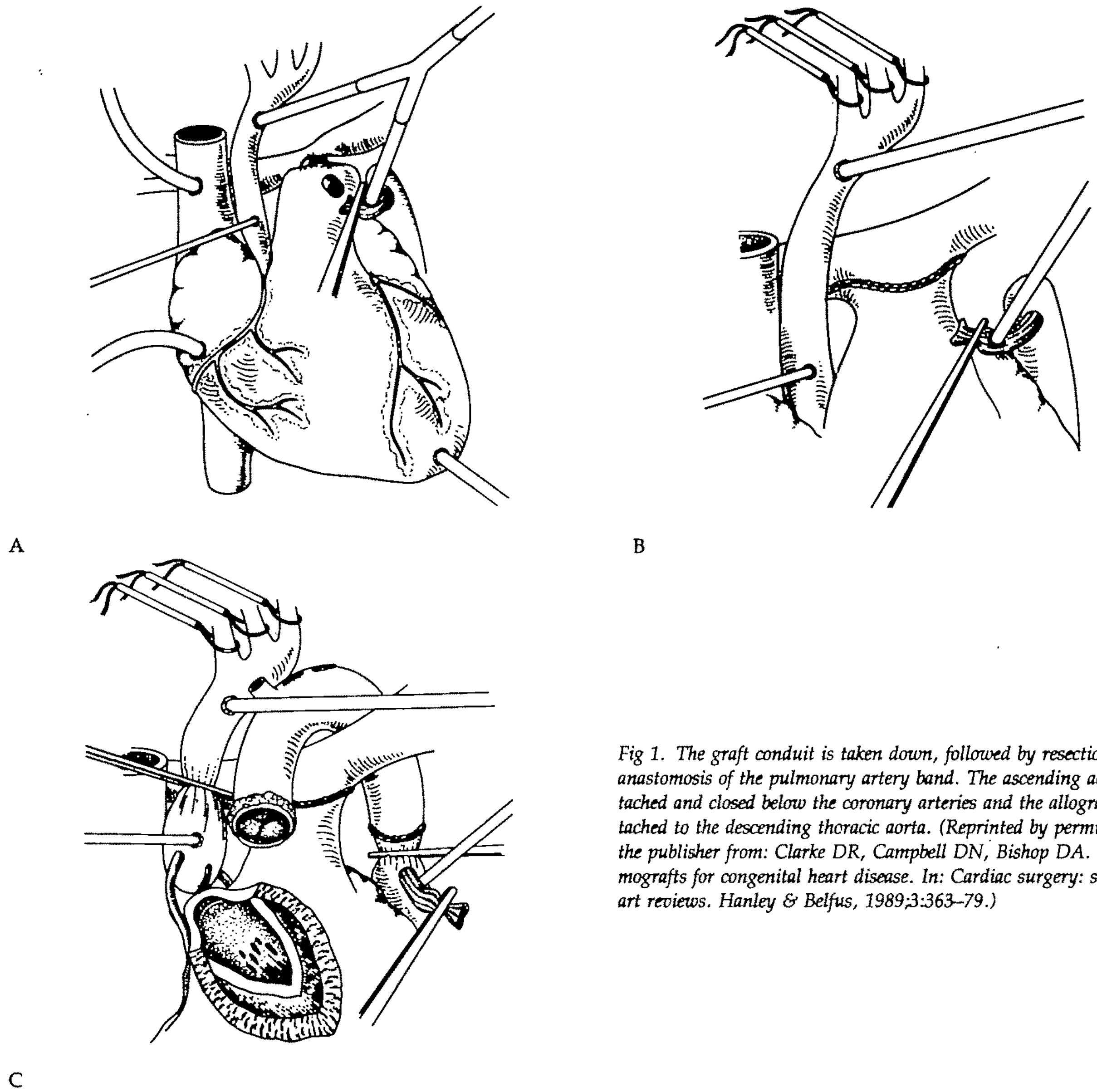

Fig 1. The graft conduit is taken down, followed by resection and reanastomosis of the pulmonary artery band. The ascending aorta is detached and closed below the coronary arteries and the allograft is attached to the descending thoracic aorta. (Reprinted by permission of the publisher from: Clarke DR, Campbell DN, Bishop DA. Homografts for congenital heart disease. In: Cardiac surgery: state of the art reviews. Hanley & Belfus, 1989;3:363–79.)

made directly opposite the allograft conduit incision. The allograft and native ascending aorta were anastomosed side to side. The cannula was removed from the distal synthetic graft; which was amputated and oversewn (Fig 2B).

The ascending aortic cannula was used to reestablish circulation, and rewarming was begun. Tourniquets were removed and warm blood cardioplegia was administered. The aortic cross-clamp was removed and cardiac rhythm returned spontaneously. A triangular patch of polytetrafluoroethylene was used to close the right ventriculotomy (Fig 2C). The child was weaned from cardiopulmonary bypass and decannulated in standard manner. Chest tubes were placed and the sternotomy was closed.

The patient's postoperative course was complicated. Multiple arrhythmias were treated unsuccessfully with digoxin, procainamide, and intermittent pacing. Control of arrhythmias was obtained with hypothermia and, later, flecainide acetate. Ventilation was problematic. Right PA stenosis had created a chronic discrepancy in right and left lung vascular resistance, and the physiologic shunt resulted in decreased oxygenation. A ventilation-perfusion study confirmed a substantial mismatch; the right lung received a majority of blood flow whereas the left lung was better ventilated. Serial chest roentgenograms revealed an elevated left hemidiaphragm that required surgical plication. Vigorous pulmonary care and nutritional support ultimately enabled the patient to be weaned from the ventilator and extubated. One year postoperatively, cardiac catheterization revealed a func-

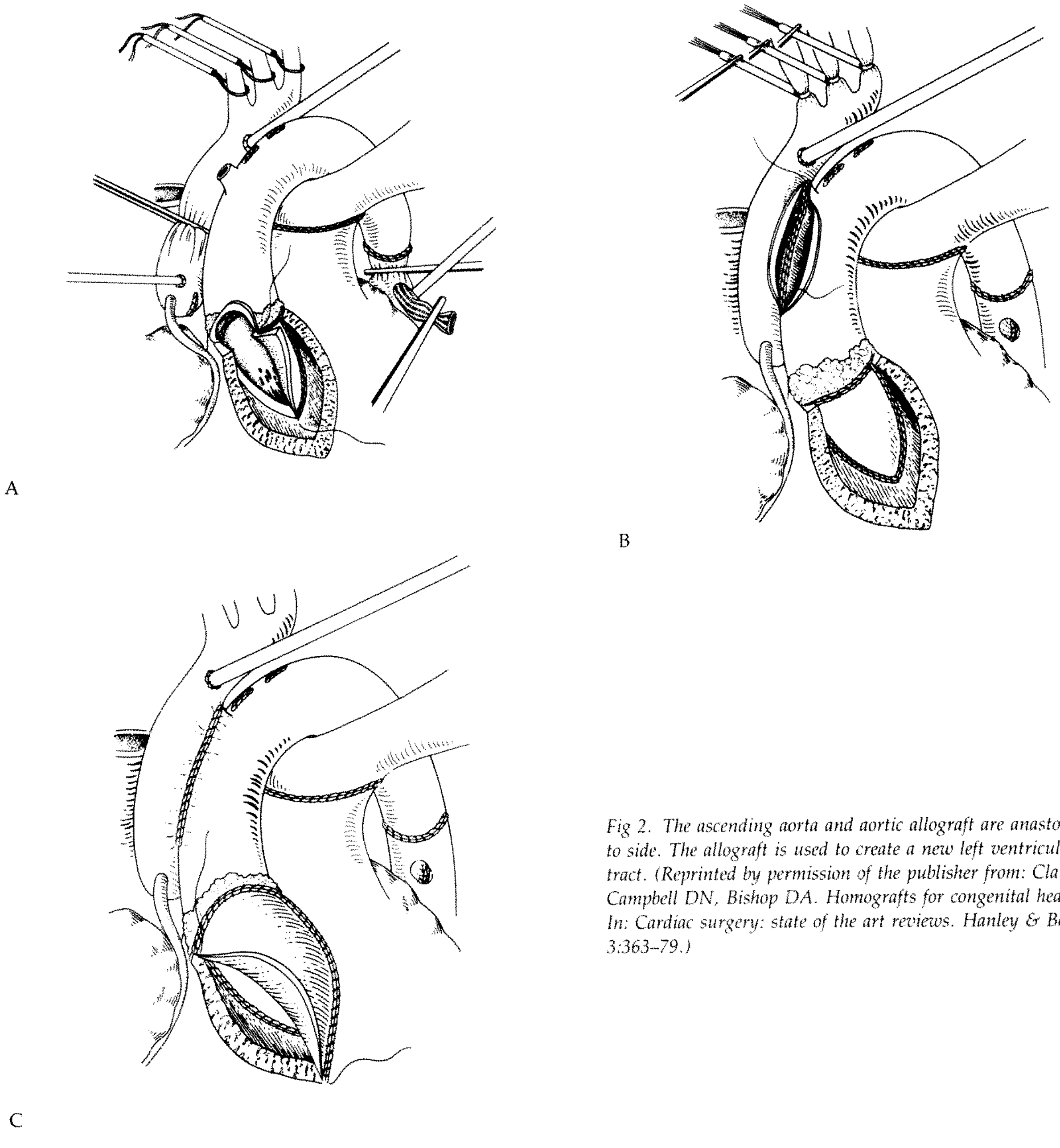

Fig 2. The ascending aorta and aortic allograft are anastomosed side to side. The allograft is used to create a new left ventricular outflow tract. (Reprinted by permission of the publisher from: Clarke DR, Campbell DN, Bishop DA. Homografts for congenital heart disease. In: Cardiac surgery: state of the art reviews. Hanley & Belfus, 1989; 3:363–79.)

tional repair. The child remains asymptomatic 34 months after operation.

Comment

Interrupted aortic arch is associated with other cardiac anomalies. Concurrent lesions include VSD most commonly, pulmonary stenosis, truncus arteriosus, or aortopulmonary window [1, 2]. A bicuspid aortic valve is present in one third of the patients [4]. The most prevalent anomaly combination consists of type B interruption of the aortic arch, VSD, patent ductus arteriosus, and left ventricular outflow hypoplasia and is considered a lethal lesion if the obstruction is severe. These children commonly are seen as neonates with severe congestive heart failure. The bleak prognosis has lead to controversy over the optimal course of medical or surgical management, both immediate and long-term.

Initial stabilization can be accomplished with prostaglandin E_1 but operation provides the only chance for long-term survival. Palliative operation generally consists of arch repair with concomitant patent ductus arteriosus ligation and banding of the PA, which provides the opportunity for subsequent growth of the left ventricular outflow tract and ascending aorta. When this does not occur, the left ventricular outflow tract remains small and requires extensive reconstruction or replacement.

Banding the main PA may distort the vessel and increase the risk of subsequent surgical procedures [5] or can aggravate existing subvalvar aortic stenosis [1]. The case herein illustrates migration of the PA band producing unilateral right PA stenosis [6]. Pulmonary arterioplasty reestablished blood flow to a low-resistance lung and resulted in unilateral pulmonary edema, ventilation-perfusion mismatch, and severe hypoxia. Stringent pulmonary care with modified postural drainage maneuvers are imperative for facilitation of ventilator management.

Complete repair in a 2-year-old child with aortic hypoplasia, VSD, and a type B interrupted aortic arch was performed using a cryopreserved aortic allograft valve conduit. Allografts have been used in the repair of cardiac anomalies since 1956 [7]. Herein their use has been extended to successfully repair a potentially lethal congenital heart lesion.

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Development of Malignant Hyperthermia During Mitral Valve Replacement

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Malignant hyperthermia is a genetically predisposed, potentially fatal disorder triggered by anesthetic agents. The early diagnosis and treatment of malignant hyperthermia is essential, yet often difficult, because the signs and symptoms of this disorder are not unique to the disease. When the patient is also undergoing cardiopulmonary bypass this disorder may be very difficult to recognize. In this article, we report a case of malignant hyperthermia diagnosed during mitral valve replacement and discuss the preoperative and postoperative management possibilities. The unusualness of this case stems from the fact that the patient had centronuclear myopathy. Although reported with other types of myopathies, centronuclear myopathy has rarely been associated with malignant hyperthermia. This episode of malignant hyperthermia was diagnosed by intraoperative measurements showing increased oxygen consumption despite hypothermic cardiopulmonary bypass.

(Ann Thorac Surg 1992;53:1114–6)

A 41-year-old, 96-kg man was seen at The Milton Hershey Medical Center with a 6-month history of increasing muscle weakness and fatigue. The muscle weakness was localized primarily in his lower extremities, but the patient did have occasional complaints of upper extremity weakness. There were no symptoms of claudication or aortoiliac insufficiency, and a neurological cause was implied. Because of an increasing number of episodes, the patient was admitted for complete neurological evaluation.

The patient's past medical history was significant for rheumatic heart disease at age 5 years and subsequent mitral stenosis requiring mitral commissurotomy 2½ years before this admission. (Just before his mitral commissurotomy, the patient developed atrial fibrillation and experienced single grand mal seizure.) Current medications were captopril, digoxin, furosemide, and warfarin sodium (Coumadin; Du Pont Pharmaceuticals, Wilmington, DE).

His physical examination was remarkable for a loud 3/4 systolic murmur and mild lower extremity edema. His neurological examination was remarkable for a weak voice, 4/5 weakness in triceps, and 3/5 global lower extremity weakness. The patient could not perform toe raises or stand from a squatting position, but otherwise his neurological examination was nonfocal.

During hospitalization, his neurological workup consisted of electromyelography, electroencephalography, and muscle biopsy, all of which were consistent with an adult form of centronuclear myopathy. Because of increasing shortness of breath and increasing symptoms of congestive heart failure, and because of his echocardiographic and recent cardiac catheterization data, mitral valve replacement was recommended. The patient had had previous anesthetic exposure, but with the history of centronuclear myopathy, an anesthesia consultation was obtained before his valvular operation. No pretreatment was recommended, although the risks of malignant hyperthermia were explained.

The patient underwent mitral valve replacement after placement of a Swan-Ganz catheter and an arterial line and use of end-tidal CO_2 monitoring. Anesthesia was induced with sufentanil and vecuronium. Just before the initiation of cardiopulmonary bypass, the patient experienced some premature ventricular contractions and mild tachycardia. This was associated with aortic and atrial cannulation and was treated with a single dose of lidocaine. No temperature elevation was noticed. The patient was noted to have some wheezing and increasing end-tidal CO_2. An aerosol bronchodilator (albuterol sulfate) was administered just before initiation of cardiopulmonary bypass.

Upon initiation of cardiopulmonary bypass and systemic cooling to 28°C, the first blood gas measurement showed the patient to be acidotic (arterial pH, 7.25; arterial CO_2 tension, 51.6 mm Hg; arterial oxygen tension, 90 mm Hg; venous pH, 7.16; venous CO_2 tension, 70.8 mm Hg; venous oxygen tension, 16 mm Hg). The aorta had been cross-clamped, and cold blood cardioplegia (4° to 8°C) at 250 to 350 mL/min had been administered for 3 minutes antegrade and topical cooling applied. Septal temperature initially fell rapidly to 12° to 15°C but within several minutes rose to more than 28°C and electrical activity resumed. Technical reasons for rapid resumption of electrical activity were searched for and ruled out. A second dose of cardioplegia was administered with an identical result. Oxygenator malfunction was addition-

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Table 1. Physiologic Data During Mitral Valve Replacement[a]

Event	Time	Temp (°C)	pH	$PaCO_2$	PaO_2	BE	PvO_2	SvO_2	VO_2
Baseline	08:28	37	7.45	37	485	+3			
CPB	09:50	27	7.34	52	77	+2	29	46	
Cooling	10:05	26	7.26	52	116	−3	35	49	144
Pre-dantrolene	10:25	22	7.22	52	90	−6	45	65	92
Post-dantrolene	10:47	24	7.33	42	404	−3	58	85	57
Rewarming	12:05	37	7.46	35	457	+2	47	83	85

[a] Oxygen consumption at 37°C was 310 $mL \cdot min^{-1} \cdot m^{-2}$.

BE = base excess; CPB = cardiopulmonary bypass; $PaCO_2$ = arterial carbon dioxide tension; PaO_2 = arterial oxygen tension; PvO_2 = venous oxygen tension; SvO_2 = venous oxygen saturation; VO_2 = oxygen consumption.

ally ruled out. The patient was resistant to systemic cooling and his serum potassium level rose from 4.1 to 5.7 mmol/L. Oxygen consumption increased as shown in Table 1. These signs and symptoms were believed to be compatible with the diagnosis of malignant hyperthermia. The patient was rapidly systemically cooled to 20°C, and dantrolene was administered. The acidosis diminished, and the arterial and venous CO_2 tensions and oxygen tensions improved. Cold blood cardioplegia was readministered as previously described, this time resulting in suitable myocardial temperature and cessation of electrical activity.

The mitral valve replacement was completed, and the patient was weaned from cardiopulmonary bypass without complications. He was transferred to the surgical intensive care unit where, approximately 6 hours postoperatively, he again had an episode of increasing temperature (39°C), increasing end-tidal CO_2, and arterial desaturation. The patient was treated with 100 mg of dantrolene and responded well. He was extubated on the second postoperative day, and the remainder of his postoperative course was unremarkable. The patient was to have an additional muscle biopsy for drug-induced muscle contractions after discharge, but has failed to follow up.

Comment

The development of symptoms of malignant hyperthermia can vary from an insidious onset to fulminant presentation. There have been very few reports of malignant hyperthermia associated with cardiopulmonary bypass operation [1, 2]. As this case illustrates, the use of cardiopulmonary bypass can further complicate the diagnosis by masking some of the signs and symptoms of this disease process. There are several aspects of anesthetic management of the malignant hyperthermia-susceptible patient that deserve comment.

First, in the preoperative period, careful anesthetic planning and awareness of the risk of malignant hyperthermia need to be explored and discussed. A patient having a family history, myopathies, and other known risk factors must be advised about the risk [3]. Prior anesthetic history, even exposure to volatile anesthetics, although important, does not ensure that the patient will not have a malignant hyperthermic reaction as demonstrated by this example. A vapor-free anesthetic machine flushed with oxygen for 48 hours, a fresh CO_2 container, and a new circuit should be employed [4]. Some centers advocate the removal of the vaporizer from the cardiopulmonary bypass machine as well [1]. Pretreatment with dantrolene ($2\ mg \cdot kg^{-1} \cdot day^{-1}$) or propofol is recommended for patients thought to be at high risk [5, 6]. Adequate premedication to sedate, minimize anxiety, and reduce stress is essential [3].

Before the induction of anesthesia, ice packs and cooled intravenous fluids should be available. Dantrolene, verapamil, sodium bicarbonate, dextrose, and insulin should also be readily available. The patient should be placed on a cooling blanket. The use of phenothiazines and anticholinergic medications may stimulate calcium release from the sarcoplasmic reticulum, create confusion regarding heart rate changes, or interfere with normal body heat loss and should be avoided [3]. Likewise, volatile anesthetics, succinylcholine, and *d*-tubocurarine are to be avoided.

During cardiopulmonary bypass, the acid-base state of the patient should be monitored every 15 minutes or by continuous on-line techniques and by arterial and venous samples. Oxygen consumption data should be calculated. In our patient, oxygen consumption before treatment with dantrolene was as much as three times the value predicted (considering patient temperature and cardiopulmonary flow rate). After treatment with dantrolene, oxygen consumption values returned to near predicted levels (Fig 1).

In the membrane oxygenator priming solution and cardioplegia, small amounts of calcium should be avoided. Moderate systemic hyperthermia of 28° to 30°C is recommended. Rewarming should be started early and slowly, taking care not to exceed 37°C, thus avoiding perioperative temperature fluctuations and minimizing malignant hyperthermic risk [7]. Vasodilator (nitroglycerin) treatment has been shown to reduce the post–cardiopulmonary bypass temperature fluctuations [8].

There is some evidence to show that malignant hyperthermia may affect cardiac muscle. In porcine cardiac preparations, physiologic abnormalities have included a

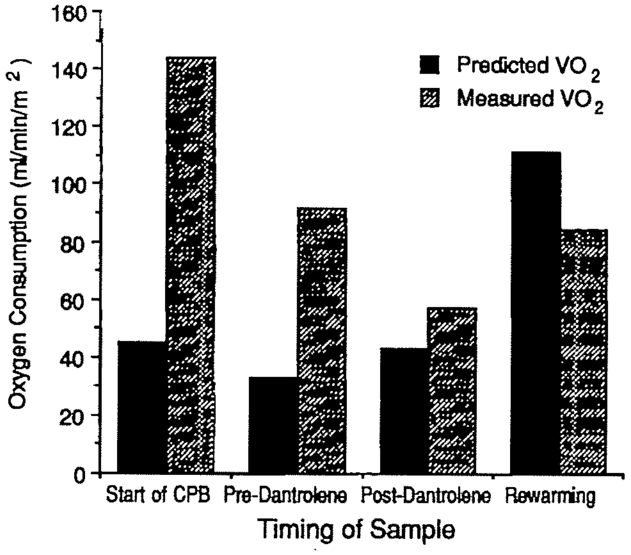

Fig 1. Comparison of predicted versus measured oxygen consumption (VO_2) for the patient during cardiopulmonary bypass complicated by the development of malignant hyperthermia. Predicted values were calculated and corrected for flow and temperature variations measured. Oxygen consumption was calculated on the basis of the Fick equation.

fivefold increase in myocardial O_2 consumption and an eightfold decrease in myocardial efficiency [9]. In our patient, until dantrolene was administered, adequate myocardial cooling and cessation of electrical activity was not achieved. Furthermore, dantrolene has been shown to depress myocardial function in animals, but no documented effect has been noted in humans [10]. Sympathetic agonists have been shown to trigger malignant hyperthermic reactions in swine, and there is a clear report of phenylephrine initiating a human malignant hyperthermic reaction [3]. The proposed mechanism of sympathetic agonist-induced malignant hyperthermia relates to muscle hypoxia resulting from decreased perfusion and acidosis. However, when a malignant hyperthermia-susceptible patient requires intropic support for weaning from cardiopulmonary bypass, the unknown risk of these agents must be accepted.

Dantrolene frequently can cause serious skeletal muscle weakness as it did in our patient. This can prolong the normal period of postoperative ventilatory support and predispose the patient to other pulmonary complications. Adequate analgesic and anxiolytic agents should be used postoperatively to minimize or reduce endogenous catecholamine response. Some groups advocate the use of pancuronium in the early postoperative period (the first 6 hours) to prevent shivering and the accompanying acidosis [7]. Otherwise, the postoperative management of the malignant hyperthermia-susceptible patient involves the same intensive care given to other cardiac patients. Any evidence of increasing temperature, acidosis, end-tidal CO_2, or oxygen consumption with or without tachycardia within the first 24 to 48 hours should be treated seriously, and dantrolene therapy may be required. Because of the high incidence of genetic susceptibility to this disease, family counseling is essential. Patients with histories of malignant hyperthermic reactions within two generations should be screened for susceptibility.

In summary, the care of a patient with preoperatively diagnosed myopathy undergoing cardiopulmonary bypass is presented. The management of these patients preoperatively, intraoperatively, and postoperatively is reviewed. If these factors are taken into consideration, the risk of cardiopulmonary bypass operation in these patients can be minimized and acceptable results obtained.

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Coronary Bypass With Both Internal Mammary and Inferior Epigastric Arteries

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A patient having undergone triple coronary artery bypass grafting with the left internal mammary artery and both shorter saphenous veins was reoperated on because of occlusion of the venous grafts. As there was no other vascular substitute available, the right internal mammary artery and both inferior epigastric arteries were used to achieve myocardial revascularization. This case demonstrates that bilateral internal mammary arteries and inferior epigastric arteries can be used safely.

(Ann Thorac Surg 1992;53:1117–9)

As the frequency of coronary revascularization procedures has increased in patients with diseased or absent greater and lesser saphenous veins, alternatives to this conduit have been sought. The inferior epigastric artery (IEA) has been advocated when traditional conduits were unsuitable [1–3]. Comparative anatomic studies showed that the internal mammary artery (IMA) is an elastic artery whereas the IEA, right gastroepiploic artery, and radial artery are muscular [4]. One great advantage of IEA over gastroepiploic artery is its availability on both sides.

A 56-year-old farmer was admitted on an emergency basis on February 1990 for unstable angina. Coronary angiography revealed diffuse triple-vessel disease. He underwent coronary artery bypass grafting on March 7, 1990. The left IMA was anastomosed to the left anterior descending artery. Because the greater saphenous veins were not available owing to bilateral long saphenous vein phlebitis, both shorter saphenous veins were used, although they were varicose. These veins were grafted onto the first obtuse marginal artery and the distal right coronary artery. Postoperative outcome was uneventful.

Two months later, this patient complained of recurrence of incapacitating angina. Coronary angiography repeated on June 19, 1990, showed a patent left IMA graft to the left anterior descending artery but occlusion of the saphenous veins implanted onto the obtuse marginal and right coronary arteries. Native coronary lesions were unchanged and were characterized by serious stenoses on the mid and distal left anterior descending arteries, the first diagonal branch, and the first obtuse marginal artery. The middle right coronary artery was occluded.

A reoperation was performed on August 6, 1990. Both IEAs were harvested through paramedian incisions following the external edge of the rectus muscles and starting at the level of the umbilicus (Fig 1). The incisions were angled as a "hockey stick" toward femoral arteries. The rectus sheath was opened throughout the length of the skin incision, and the rectus muscle was dissected from its external bed and retracted medially. The IEAs were harvested as a pedicle with the two accompanying veins, starting at their origin from the external iliac artery. The rectus sheath incision was repaired with interrupted stitches, and vacuum drainage was started. Resternotomy was performed cautiously to avoid damaging the anastomosed left IMA. The right IMA was dissected free. The ascending aorta was cannulated and cardiac drainage was obtained by cannulating the right atrium with a two-stage cannula. The aorta was cross-clamped and crystalloid cardioplegia was administered into the aortic root. Cardioplegia was repeated after completion of each distal anastomosis. Minimal rectal temperature was 22.7°C. The first IEA was grafted to the first obtuse marginal branch beyond the previous venous anastomosis. The right IMA was anastomosed to the posterior descending artery, and the second IEA was implanted onto the first diagonal branch (Fig 2). Anastomoses were realized with 8-0 polypropylene and 3.5 times magnification. Proximal anastomoses of the IEAs were realized during aortic cross-clamping, the graft supplying the diagonal artery being implanted on the origin of a previous saphenous vein graft (7-0 polypropylene running suture) and the second IEA being sutured directly to the aortic wall (6-0 polypropylene running suture). Duration of aortic cross-clamping was 159 minutes, and total duration of cardiopulmonary bypass was 255 minutes.

Postoperatively, the transient pulmonary edema developed. An increase in the level of the creatine-kinase isoenzyme MB to 61 IU/mL was observed 10 hours after the procedure (maximum, 50 IU/mL), followed by a decline toward normal values (29 and 15 IU/mL at 34 and 58 hours, respectively). However, there was no electrocardiographic sign of new-onset myocardial infarction or ischemia. No specific pharmacological protocol for pre-

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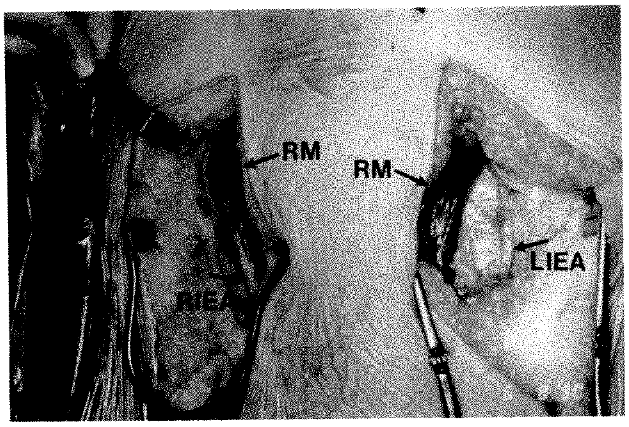

Fig 1. Bilateral dissection of the inferior epigastric arteries through paramedian incisions. (LIEA = *left inferior epigastric artery;* RIEA = *right inferior epigastric artery;* RM = *rectus muscle.)*

venting postoperative arterial spasm was used. There was no complication related to the harvest of the IMAs or the IEAs.

Angiographic follow-up was performed on February 5, 1991 (6 months later). Both IMAs were patent. The IEA anastomosed to the first diagonal artery was patent (Fig 3). The ostium of the IEA grafted onto the obtuse marginal artery could not be found, the graft being possibly occluded.

This patient is angina-free at the present time, 20 months after his last procedure.

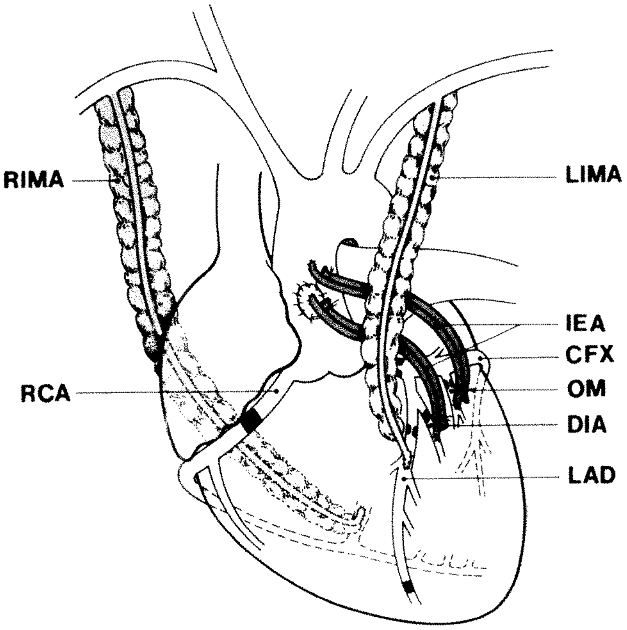

Fig 2. Grafting of both internal mammary and inferior epigastric arteries. (CFX = *circumflex artery;* DIA = *diagonal branch;* IEA = *inferior epigastric artery;* LAD = *left anterior descending artery;* LIMA = *left internal mammary artery;* OM = *obtuse marginal artery,* RCA = *right coronary artery;* RIMA = *right internal mammary artery.)*

Comment

Since the first IEA grafting performed at our institution on December 16, 1988 [1], 83 free IEAs were used in 82 patients for coronary artery bypass grafting in combination with IMA grafts. Sixty-nine patients underwent angiographic study 10 days after operation: 98% of the IEA grafts were patent. An angiographic study obtained at 6 months in 27 patients showed an 88% patency rate. Our indications for the use of the IEA are the absence of suitable saphenous vein, IMA, or both and attempt to realize complete arterial revascularization in young patients. In the present case, the left IMA had been used and no saphenous vein was available. An alternative to the use of IEA was the right gastroepiploic artery. However, the right gastroepiploic artery provided only one arterial conduit whereas two more arteries needed grafting.

Combined harvest of both IEAs and both IMAs might theoretically involve a risk of abdominal wall necrosis. Nevertheless, in the absence of both IMAs and IEAs, a vascular supply to the abdominal muscles remains through lumbar, deep, and superficial circumflex iliac and superficial epigastric arteries. Indeed, the main vessels that feed the abdominal wall from below are the IEA and the deep circumflex iliac arteries [5, 6]. Both arise from the external iliac artery. The next three arteries participating in the blood supply of the abdominal wall stem from the femoral artery and are the superficial epigastric, superficial circumflex iliac, and external pudendal arteries. The lumbar arteries anastomose with the lower intercostal, iliolumbar, and superior and inferior epigastric arteries and with the ascending branch of the deep circumflex iliac artery. Furthermore, the superior epigastric artery, one of the terminations of the IMA, anastomoses freely with the inferior epigastric artery in only 40% of the cases [6]. These anatomic considerations may explain the absence of

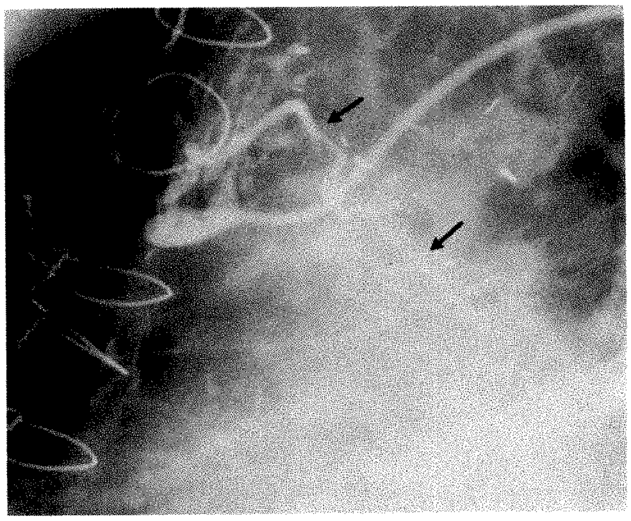

Fig 3. Coronary angiogram (left lateral view) showing a patent free inferior epigastric artery (arrows) *anastomosed to the first diagonal branch.*

abdominal wall complications even after extensive harvest of bilateral mammary and epigastric arteries.

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Notice From the American Board of Thoracic Surgery

The part I (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas, TX, on February 7, 1993. The closing date for registration is August 1, 1992.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

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Right Latissimus Dorsi Cardiomyoplasty for Left Ventricular Failure

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Recent experimental studies have shown that cardiomyoplasty using the right latissimus dorsi provides excellent hemodynamic augmentation. Based on these experimental findings, this procedure was performed in a 40-year-old man with a dilated cardiomyopathy after a large myocardial infarction. The patient tolerated the procedure well and has had marked functional improvement. Examination 6 months after operation demonstrated decreases in right atrial pressure, pulmonary capillary wedge pressure, and left ventricular end-diastolic volume. In addition, increases were noted in cardiac output, stroke volume, left ventricular stroke-work, right ventricular ejection fraction, and left ventricular ejection fraction. Because of this promising clinical result, we have started a series of right latissimus dorsi cardiomyoplasties for left ventricular failure.

(Ann Thorac Surg 1992;53:1120–2)

The left latissimus dorsi has been used for cardiomyoplasty in previous clinical attempts to improve left ventricular function. Experimental studies from our laboratory have demonstrated that cardiomyoplasty using the right latissimus dorsi has greater hemodynamic effects than that done using the left muscle [1]. Based on these experimental findings, a right latissimus dorsi cardiomyoplasty was performed in a patient. This report outlines the case history, operative technique, and results of right latissimus dorsi cardiomyoplasty for left ventricular failure.

A 40-year-old man was well until 1 year before referral to our institution, when he suffered a large anterior myocardial infarction complicated by cardiogenic shock. An intraaortic balloon pump was placed and he made a slow recovery. Cardiac catheterization demonstrated occlusion of the proximal left anterior descending coronary artery, but the right and circumflex coronary arteries were normal. His past medical history was significant only for a 60-pack-year history of smoking.

The patient was advised by his physician to undergo evaluation for cardiac transplantation. He declined this option and referred himself to be evaluated for cardiomyoplasty. The results of his multigated acquisition radionuclide scan and cardiac catheterization are shown in Table 1. Selective coronary angiography confirmed the previous catheterization findings. The echocardiogram showed a large, poorly contractile left ventricle but no serious mitral or tricuspid regurgitation. A stress thallium study showed a large anterior area without uptake compatible with the history and catheterization findings. There was no ischemia. Holter recordings demonstrated mild to moderate polymorphic ventricular ectopy but no episodes of sustained ventricular tachycardia. Pulmonary function test results were normal. The patient's medications were digoxin, 0.25 mg/day, and enalapril, 5 mg once per day. He was well compensated on medical therapy despite the impaired left ventricular function, and was considered in New York Heart Association functional class II. Because of his young age, enlarged heart, and poor left ventricular function, surgical intervention was recommended. Because of his desire to avoid transplantation, he was scheduled for cardiomyoplasty.

The operative procedure was done in two stages separated by 3 days [2]. The right latissimus dorsi muscle was mobilized from the subcutaneous tissue through a long flank incision. Two intramuscular pacing leads (model SP5528; Medtronic, Inc, Minneapolis, MN) were implanted, the cathode near the entry of the thoracodorsal neurovascular bundle into the muscle, and the anode 6 cm distally. Three days later the flank incision was reopened. The origin and insertion of the muscle were divided, a 5-cm portion of the anterior right third rib was resected, and the muscle was placed in the right hemithorax. The tendon of the muscle was then sutured to the chest wall in the bed of the resected rib segment.

A sternotomy was made, the pericardium was opened, and the muscle was retrieved from the right hemithorax. A sensing lead (model 6917A; Medtronic, Inc) was attached to the right ventricle. The muscle was brought across the heart anteriorly and then sutured to the posterior pericardium at the level of the atrioventricular groove using interrupted, pledgeted sutures of 2-0 Ticron (Davis + Geck, Danbury, CT). No sutures were placed in the myocardium. The suture line started just caudal to the left pulmonary artery and ended adjacent to the inferior vena

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Table 1. Hemodynamics Before and After Right Latissimus Dorsi Cardiomyoplasty

Variable	Preoperative	Six Months Postoperative (pacing 1:1)
CO (L/min)	5.9	7.9
SV (mL)	78	96
LVSW (g-m)	57	74
RA (mm Hg)	7	3
PA (mm Hg)	40/26	26/11
PCW (mm Hg)	24	15
LVEDP (mm Hg)	20	18
MAP (mm Hg)	78	72
RVEF	0.56	0.65
LVEF	0.23	0.34
LVEDV (mL)	422	346

CO = cardiac output; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVSW = left ventricular stroke work; MAP = mean arterial pressure; PA = pulmonary artery pressure; PCW = pulmonary capillary wedge pressure; RA = right atrial pressure; RVEF = right ventricular ejection fraction; SV = stroke volume.

cava (Fig 1). Transient hypotension resulted when the heart was retracted to place the sutures in the pericardium. Extracorporeal circulation was not used but was available on short notice. The muscle was positioned so that the costal surface of the muscle covered both ventricles. The pacing and sensing leads were connected to the Medtronic SP1005 cardiomyostimulator, which was buried in a subrectus pocket in the anterior abdominal wall.

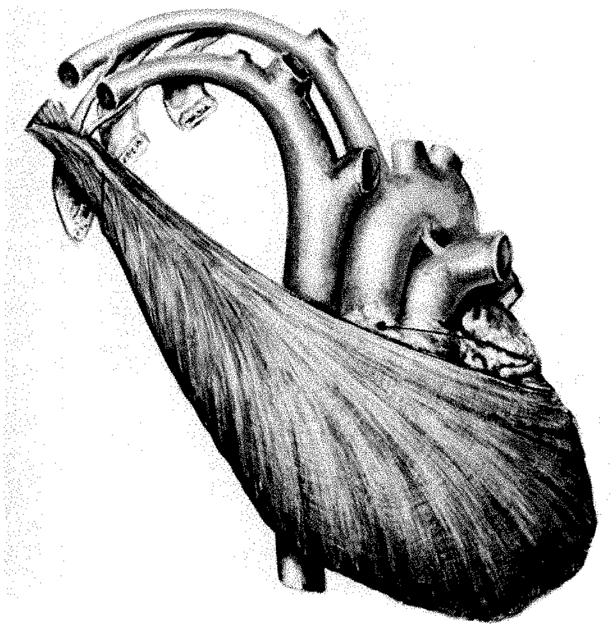

Fig 1. The right latissimus dorsi is brought anteriorly across the heart and covers the entire ventricular mass. Contraction of the muscle pulls the left ventricle toward the right shoulder.

The patient tolerated the procedure well and was able to be extubated the next day. Cardiac function was excellent without the need for intravenous inotropes or an intraaortic balloon pump. Four days later he required reintubation because of inability to clear thick pulmonary secretions. He remained intubated for the next 5 days, but thereafter made a rapid recovery and was discharged from the hospital 18 days after cardiomyoplasty.

Stimulation of the muscle was started 10 days after operation. Conditioning of the muscle was done using a protocol previously published, which consists of gradually increasing periods of stimulation alternating with periods of rest [3].

The patient made rapid progress after hospital discharge and resumed full activity with no limitations within 2 months of operation (New York Heart Association class I). His only medications were digoxin and enalapril in the same doses that he was taking preoperatively. Six months after the original operation he returned for cardiac catheterization, multigated acquisition radionuclide scan, and echocardiography. The cardiomyoplasty was being stimulated at a ratio of 1:1 with the native heart. The cardiomyostimulator settings were an amplitude of 4 V, pulse train duration of 185 ms, pulse train frequency of 33 Hz, and delay cardiomuscular period of 75 ms. Marked reductions in right atrial, pulmonary artery, pulmonary capillary wedge, and left ventricular end-diastolic pressure were measured. Increases in cardiac output and right and left ventricular ejection fraction were also noted (see Table 1).

Comment

The operative technique of right latissimus dorsi cardiomyoplasty for treatment of left ventricular failure differs only slightly from that used for the left cardiomyoplasty. Both procedures involve a flank incision to mobilize the muscle and a median sternotomy to complete the muscle wrap. The only major differences are in the placement of the muscle on the heart and in the proposed mechanism of its action. The left latissimus cardiomyoplasty requires circumferential wrapping of both ventricles to allow a theoretical squeezing action of the heart. The right latissimus cardiomyoplasty fixes the muscle to the heart at the level of the atrioventricular groove, which causes a linear pulling force on the left ventricle when the muscle contracts.

A marked improvement in functional status and an objective improvement in ventricular function were noted in this patient. He swims regularly for exercise and has no limitations in daily activities. Follow-up cardiac catheterization has shown decreases in cardiac filling pressures and increases in cardiac output and ejection fraction. This has resulted in a large increase in left ventricular stroke work. The reduction in left-sided filling pressures has resulted in a decrease in the pulmonary artery pressure, which has lowered the stroke work of the right ventricle and allowed improvement in right ventricular ejection fraction. These changes are consistent with the hemodynamic changes previously demonstrated in experimental animals [1].

Echocardiography showed improved motion of the anterior and lateral walls of the left ventricle with stimulation of the right latissimus dorsi muscle. The right cardiomyoplasty pulls the left ventricle toward the right shoulder, which is parallel to the net vector of flow in the left ventricle. When the left cardiomyoplasty contracts, it pulls the ventricles toward the left shoulder, which is perpendicular to the direction of flow through the aortic valve. Consequently the right cardiomyoplasty appears to have a better geometric configuration for assisting contraction of the left ventricle. In addition, cadaver studies have shown that the right latissimus dorsi is approximately 25% larger than the left [4]. It seems probable that these factors account for the improved hemodynamic effects seen in this case. However, additional investigation in more patients will be necessary to confirm this hypothesis and to evaluate other possible mechanisms. Because of the promising experimental and clinical results, we have started a clinical series using the right latissimus dorsi to augment left ventricular function.

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Percutaneous Localization of Pulmonary Nodules for Thoracoscopic Lung Resection

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A limiting factor in removing pulmonary nodules by videothoracoscopic techniques is the inability to locate lesions deep within the substance of the lung. We describe a technique in which a hook wire commonly used to localize nonpalpable breast lesions is placed percutaneously into the lung nodule preoperatively. Using the wire anchored into the lung as a guide, the target lesion can be successfully identified and removed thoracoscopically.

(Ann Thorac Surg 1992;53:1123–4)

The recent advancements in endoscopic instrumentation and techniques have broadened the application of thoracoscopy [1]. Lung resection for solitary pulmonary nodules is now possible by videothoracoscopic techniques [2]. Because of difficulty in localizing pulmonary nodules by palpation through a thoracoscope, resection is generally limited to those nodules that are attached to the visceral pleura or are immediately subpleural. Although resection of deeper pulmonary nodules is technically possible, identification of the location of the lesion in the lung remains a limiting factor.

Percutaneous localization of nonpalpable breast lesions discovered at mammography has been widely practiced for at least 15 years [3, 4]. We recently have applied this technique successfully to lung nodules that we anticipated having difficulty locating at the time of thoracoscopy.

Technique

Once a pulmonary nodule has been identified and the patient has been deemed to be a candidate for removal of the lesion by thoracoscopy, a determination is made regarding the likelihood of being able to locate the lesion endoscopically. If it is believed that the lesion is unlikely to be identified from the pleural surface by visual inspection or palpation with an instrument, the patient is taken to an x-ray suite where the location of the lesion is determined either fluoroscopically or by computed tomographic scan. A needle from the localizer system (Sadowsky Breast Marking System; Ranfac Corporation, Avon, MA) is then placed percutaneously through the chest wall into the pulmonary nodule. Its accurate placement is then ascertained by viewing the location of the needle from multiple angles, either fluoroscopically or by computed tomographic scan (Figs 1, 2). Once it is determined that the tip of the needle is in the nodule, the hook wire is then advanced through the 20-gauge needle into the lesion and the needle is withdrawn, leaving the wire in position through the skin. We have also injected 0.05 mL of methylene blue through the localizing needle before insertion of the hook wire as an additional aid in localizing the nodule [5]. The patient is then transported to the operating suite.

The patient is given a general anesthetic with a double-lumen endotracheal tube and put in a lateral decubitus position. The localizing wire is *not* fastened to the chest wall. A 10-mm endoscope is placed through a trocar, and the entry site of the hook wire into the lung is identified.

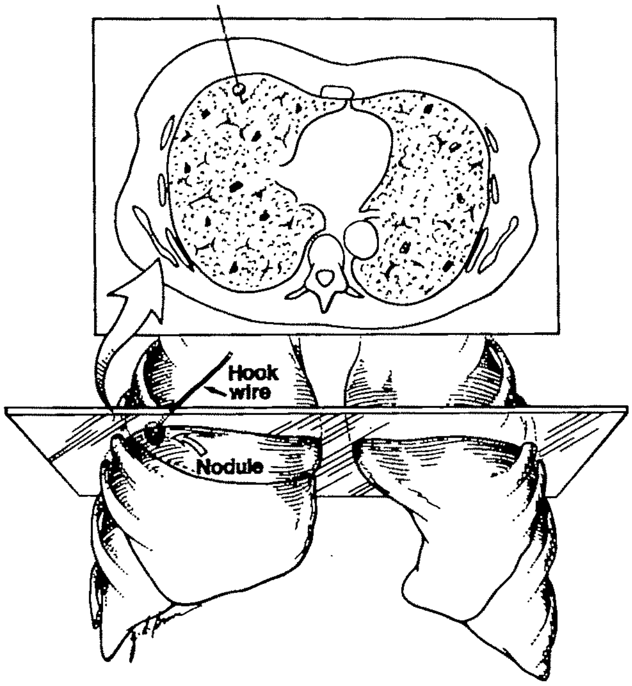

Fig 1. Localization of small pulmonary nodule by hook wire.

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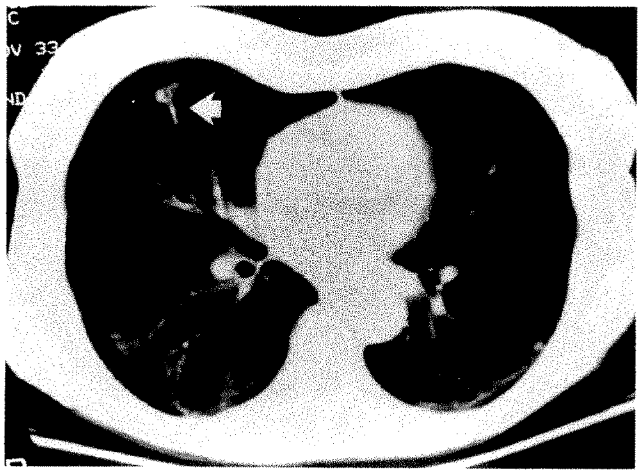

Fig 2. Computed tomographic scan demonstrating end of hook wire through nodule (arrow).

Using a laser (argon or neodymium:yttrium-aluminum garnet), a circumferential score is made on the visceral pleura around the wire (Fig 3). A core of lung tissue is developed by the laser as described by Landreneau and associates [2] until the nodule with hook wire imbedded in it is removed through the largest portal available.

Results

Using this technique, we have accurately identified nine pulmonary nodules in 6 different patients. There was no visible evidence of the presence of the nodule beneath the pleural surface except for the hook wire leading to it, nor was the lesion palpable by "feeling" the lung with endoscopic instruments.

All nine nodules were removed with adequate surgical margins present. Two lesions were primary lung cancers in patients with poor pulmonary reserve. Two patients had metastatic nodules from colon carcinoma removed. The fifth patient had four bilateral 6-mm subpleural nodules with a primary malignant melanoma (level IV) of the back. Two nodules in the right lung were excised as a staging procedure. Pathology revealed lymphoid aggregates in the lung. The last patient had multiple small nodules after autologous bone marrow transplantation for refractory Hodgkin's disease. Biopsy of the lung nodule revealed recurrent lymphoma.

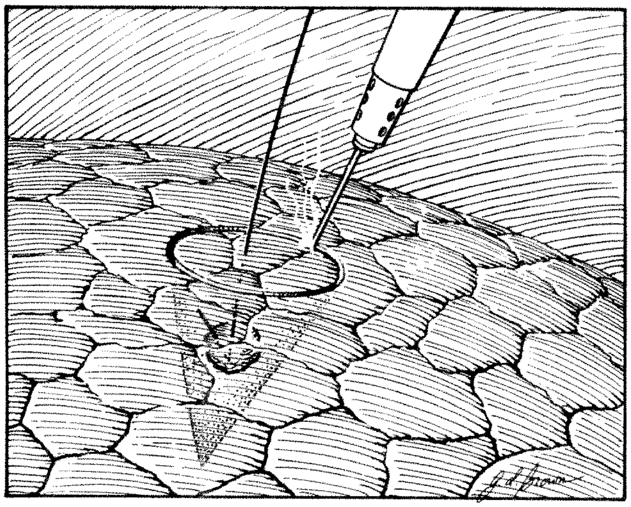

Fig 3. Neodymium:yttrium-aluminum garnet laser scoring surface of lung overlying nodule.

Comment

Expanding the application of thoracoscopic instrumentation and techniques, we have performed 48 lung resections for suspicious peripheral pulmonary lesions. A major factor limiting the success of thoracoscopic resection of the lung is the inability to locate the target pulmonary nodule, either by puckering of the visceral pleura by the lesion or by effacement of its margins against the surrounding collapsed atelectatic lung parenchyma.

We have attempted a number of maneuvers to locate the lesion with varying degrees of success. These included running instruments over the surface of the lung to indirectly "feel" it beneath the pleural surface, placing a finger through a trocar site to directly palpate the lung, and percutaneously injecting methylene blue under fluoroscopic guidance into the lung over the lesion.

From our early experience with radiologic-assisted, percutaneous hook wire localization of small peripheral lung lesions, we have found that it is easy to perform and has allowed for complete removal of the occult peripheral lung lesion. Although our numbers are small, this technique has not resulted in any unexpected morbidity.

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Technique for Replacing the Ascending Aorta and Aortic Valve With a Modified Bentall's Operation

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Composite graft replacement of the aortic root and valve poses the challenge of reimplanting both coronary ostia. The technique of sandwiching the freed button of aortic wall bearing the coronary artery ostium between an outer Teflon felt washerlike buttress and the inner composite graft provides a leak-proof anastomosis while reestablishing direct graft to coronary artery continuity regardless of the location of the coronary ostia or type of root pathology.

(Ann Thorac Surg 1992;53:1125–6)

Following Bentall and DeBonno's report [1], replacement of the ascending aorta and aortic valve with a composite graft by inclusion technique has gained acceptance as the management of choice in various disorders. On the other hand the number of reported technical modifications [2–8] underscores the difficulties and problems related to the coronary reimplantation. Two modifications have proved to be most effective, namely, the interposition of a graft between the coronary artery ostium and the prosthetic graft [5, 6] and the freeing of an aortic button bearing the coronary artery ostium [7, 8]. A technique of sandwiching the aortic wall button bearing the coronary ostium, which has proved to be leak-proof, has been developed and used since 1982 in 67 consecutive patients with a variety of aortic root pathology and is herein described.

Technique

Extracorporeal circulation is established by arterial return to one femoral or external iliac artery and by single atrial or bicaval cannulation. Moderate systemic hypothermia (27° to 28°C rectally) is induced. When ventricular fibrillation occurs, the aorta is cross-clamped, a vertical aortotomy is extended toward the noncoronary sinus, and the edges of the aortotomy are suspended with traction sutures. Myocardial protection is achieved with hyperkalemic, substrate-enriched blood cooled to 8° to 10°C selectively perfused antegradely into each coronary artery, or retrogradely into the coronary sinus, every 30 minutes, as well as topical cooling.

The aortic valve cusps are excised or left intact to be used as part of the buttressing material; annular everting horizontal mattress sutures of 1-0 polyester bolstered with Teflon felt pledgets to secure the composite valve in the juxtaannular position are placed. While the composite graft soaked in human albumin is autoclaved for 5 minutes, the left coronary button is prepared first by starting the dissection close to the commissure between the left and the noncoronary sinus and carrying the incision around the bottom of the left sinus of Valsalva 6 to 8 mm away from the coronary ostium (Fig 1A). The right coronary button is prepared next by starting the dissection at the commissure between the right and the noncoronary sinus, incising the bottom of the right sinus of Valsalva 6 to 8 mm away from the coronary ostium. The previously placed annular sutures are passed through the valve sewing rim of the composite graft, which is securely tied in place. A circular buttonhole 10 to 12 mm in diameter is made in the graft just opposite to the left coronary ostium. A washerlike or doughnutlike buttress is made out of a circle of 3 cm diameter and 1.0 mm thick Teflon felt with an orifice larger than the graft buttonhole. The aortic button bearing the left coronary artery is passed through the orifice of the felt washer, and interrupted horizontal mattress sutures of 3-0 or 4-0 polyester are placed so as to sandwich the aortic button between the outer felt washer and the inner composite graft. The sutures are passed through the aortic button about 2 to 3 mm from the coronary ostium per se, and 1.0 mm from the hole edge of the washer and graft buttonhole. The lower three or four sutures are placed outside-in to be tied within the lumen of the graft (Fig 1B), whereas the remaining five to eight sutures are placed inside-out to be tied on the outer surface of the felt washer (Fig 1C). All sutures are placed before any of them are tied. Blood cardioplegic solution is perfused through the temporarily closed distal end of the composite graft at 80 to 100 mm Hg pressure and the anastomosis is tested for any leak, which if present can be corrected easily at this point. The right coronary button is anastomosed and tested in a similar manner (Fig 1D). Rewarming of the patient is initiated near the completion of the coronary reimplantation.

The aorta is transected distal to the aneurysm, leaving a generous cuff. The tubular graft is anastomosed to the distal aorta by telescoping the graft into the true lumen of such cuff and sandwiching the aortic wall between the inner telescoped graft and an outer periaortic buttressing Teflon felt strip of 10 to 15 mm in width, using interrupted sutures of 2-0 or 3-0 polyester. The bottom four sutures are placed outside-in to be tied inside the graft lumen, whereas the remaining sutures are placed inside-out to be

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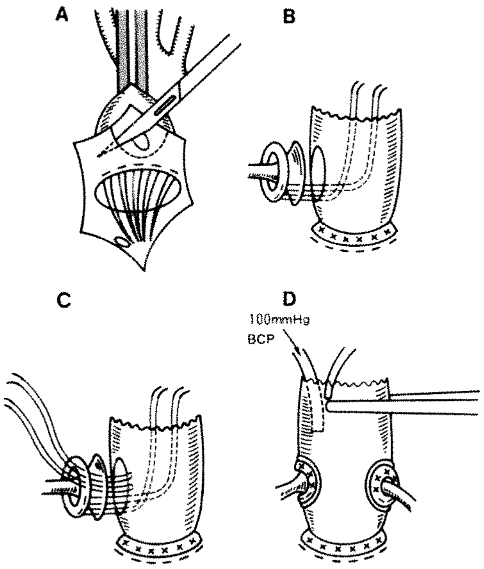

Fig 1. Essential steps for coronary reimplantation during composite-valve replacement of the aortic root. (A) Freeing and excision of the left coronary artery ostium–bearing aortic button, retaining at least 5 to 10 mm of aortic wall surrounding the ostium. (B) Placement of the bottom interrupted sutures from the outside-in, sandwiching the coronary artery–bearing aortic button between an outer washerlike buttressing Teflon felt and the inner vascular graft of the composite prosthesis. (C) Placement of the remaining sutures from the inside-out. All sutures around the button are placed before any of them are tied. (D) Testing of both coronary reimplanting suture lines by infusing blood cardioplegic solution (BCP) at 80 to 100 mm Hg pressure before anastomosing the vascular graft to the distal aorta.

tied on the external surface of the felt strip (Fig 2). All sutures are placed before any of them are tied. Warm blood cardioplegic solution is infused through the composite graft to check for any bleeding for the last time. The aortic cross-clamp is removed. The usual debubbling maneuvers are performed by connecting the cardioplegia administration needle placed in the composite graft to the cardiotomy suction line while maintaining the aorta or the graft partially clamped (60% to 70% of its folded width) downstream to such needle and allowing the left ventricle to eject. Only after hemostasis is completed is the aneurysmal aortic wall tailored to provide a fit cover around the graft.

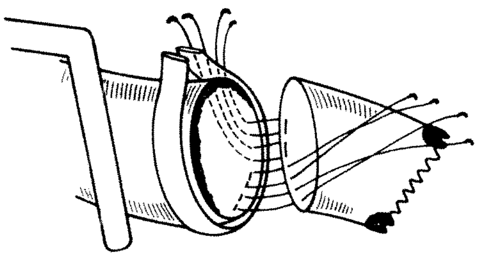

Fig 2. Distal graft to aorta anastomosis sandwiching the aortic wall between an outer circumferential Teflon felt strip and the inner telescoped vascular prosthesis. The four bottom sutures are placed from the outside-in, and the remaining sutures from the inside-out.

Comment

Although a split washer has been placed without making aortic buttons in a few patients with displaced coronary artery ostia, fashioning free aortic buttons bearing the coronary ostium facilitates the dissection around the coronary artery as well as placing of the sutures for a tension-free anastomosis even with a continuous suture as described by Kouchoukos and associates [7] and Iglesias and co-workers [8], regardless of the distance from the annulus or the underlying pathology. It offers the advantage of not requiring any interposition graft material. However, when the pericoronary aortic wall is friable, such simple suturing technique might be complicated by acute disruption when the aorta is unclamped [8]. The described sandwiching technique for all anastomoses, ie, coronary buttons and distal aorta, requires a slightly longer aortic cross-clamp time, usually in the range of 150 to 170 minutes, but it has proved to be leak-proof in 67 consecutive patients in whom 60 left and 57 right coronary ostia have been reimplanted, even in patients with acute aortic dissection with infracoronary intimal tear or dissection extending into the left or right coronary artery origin or rupturing one of the sinus of Valsalva, in patients requiring coronary ostial endarterectomy, or in patients with aortitis on steroid therapy. Although 4 patients required reexploration for postoperative bleeding, in none was it related to any of the anastomotic lines, and no late pseudoaneurysms or fistulas have developed. Perigraft aortic wall wrapping or creation of a fistula between the aortic wrap and the right atrium to control the troublesome perigraft hematoma formation are not required "tricks."

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A Simple and Safe Technique of Left Ventricular Venting

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Left ventricular venting has many physiologic and practical benefits. A venting technique is described that employs a simple, closed system which allows the perfusionist to monitor left ventricular distention. By monitoring the left ventricular volume the perfusionist can regulate the degree of negative pressure on the vent and thus reduce the chance of air entering the heart.

(Ann Thorac Surg 1992;53:1127–9)

The advisability of venting the left ventricle during coronary artery bypass operations remains controversial. We have consistently employed a left ventricular vent ever since a clinical study found better left ventricular performance immediately after coronary bypass operations in which a vent was used [1]. Furthermore, we have believed that the vent provides maximum benefit if the catheter vents the left ventricle directly, rather than indirectly through the pulmonary artery, as a direct left ventricular vent can prevent left ventricular distention even in the presence of considerable aortic regurgitation and a competent mitral valve. Surgeons who avoid venting the left ventricle during routine coronary bypass operations express concern about unnecessary complexity and the potential for introducing air into the left ventricle.

We describe herein a method of venting the left ventricle that we have used routinely in more than 4,000 coronary bypass operations over the past 7 years. Vent suction is maintained by a siphon effect within a completely closed system, and the risk of introducing air is minimal. The perfusionist adjusts the amount of negative pressure by changing the height of a collapsible reservoir. Roller pumps, needle vents, three-way valves, and other adjuncts are unnecessary, but a roller pump is part of a shunt in the circuit and can be activated immediately when required.

Technique

After placement of standard aortic and right atrial cannulas and initiation of cardiopulmonary bypass, the right superior pulmonary vein is exposed. A pledgeted pursestring suture (2-0 Ethibond; Ethicon, Somerville, NJ) is placed in a triangular configuration, which is more airtight than a mattress suture. The venous drainage is temporarily impeded to fill the heart partially and to prevent air from entering the heart; a stab wound is made in the pulmonary vein, and the vent is passed into the left ventricle.

In preparation for the maneuvers already mentioned, the vent circuit is first primed with saline solution from the surgical field by applying suction with the roller pump. The circuit consists of ¼-inch tubing draining from the surgical field to a Y connector at the pump, which directs flow to either a collapsible plastic bag or to a roller pump head. The collapsible plastic bag is simply an empty bag from intravenous fluid that was used for priming the oxygenator. The outlet side of the plastic bag reservoir and the output of the roller pump both go to another Y connector to allow drainage of either the collapsible bag or the roller pump into the filtered portion of an integrated venous/cardiotomy reservoir (Fig 1). Under ordinary circumstances, the shunt through the roller pump head is clamped; the plastic bag is the vent reservoir. The collapsible bag is hung on a pole with a sliding hook, and it can be raised or lowered to adjust the amount of gravity siphon.

The volume of blood in the collapsible bag is determined by the volume in the left ventricle. By monitoring the volume in the bag, the perfusionist can adjust the gravity siphon to maintain a constant small volume in the bag, thus keeping the heart empty without drawing air into the left ventricle. In most instances, it is unnecessary for the surgeon to communicate with the perfusionist about the level of suction that is needed. When unusually large amounts of suction are needed (eg, in the presence of aortic regurgitation), active suction can be applied to the vent. The two options for drainage are described more fully in the next two sections.

Gravity Drainage

With the height of the collapsible bag kept equal to or slightly lower than the height of the heart, blood in the left ventricle will "seek its own level" with the blood in the bag (see Fig 1). If the left ventricle is empty the vent bag will remain empty. If the left ventricle starts to distend, the vent bag will also start to distend. Because the volume in the heart is represented by the volume in the bag, cardiac distention is always apparent to the perfusionist, who can then adjust the siphon by lowering the bag. The surgeon is not distracted by the need to give instructions regarding the vent.

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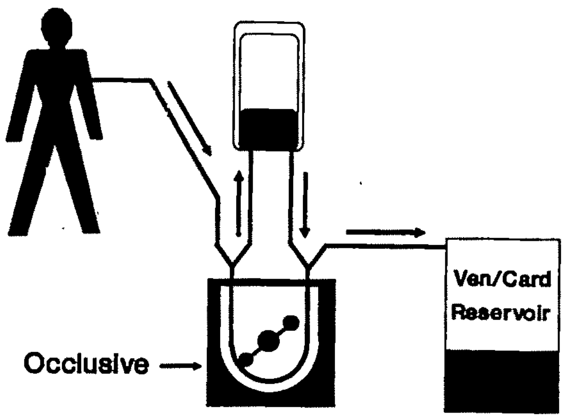

Fig 1. When the circuit is used with gravity drainage, no clamps are applied to it. The roller pump is set to be just occlusive and is turned off. Drainage follows a path from the heart to the collapsible reservoir bag and into the venous/cardiotomy reservoir. The height of the bag can be adjusted to increase or decrease the siphon on the left ventricle.

Suction Plus Gravity Drainage

When the blood volume entering the heart exceeds the capacity of the vent to remove it by gravity drainage, additional suction is applied (Fig 2). This is accomplished without the loss of the perfusionist's ability to monitor the volume in the left ventricle by simply applying roller pump suction to both the vent bag and the left ventricle simultaneously. A clamp is placed on the outlet side of the bag, but no clamps are applied to the inlet side of the circuit so that the pump is drawing equally from the bag and from the heart. The pump speed is simply regulated to keep the vent bag and the heart empty or nearly so, without generating excessive negative pressure.

Before discontinuation of cardiopulmonary support, the left ventricular vent is removed and is replaced with a left atrial catheter (Intracath 16-gauge, 61 cm; Becton Dickinson, Sandy, UT) to measure left atrial pressure. This catheter is removed in the intensive care unit on the first or second postoperative day before the chest tubes are removed.

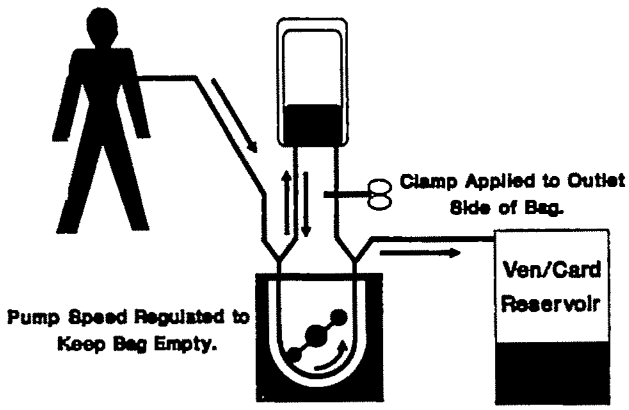

Fig 2. When suction needs to be applied, a clamp is placed on the outlet side of the collapsible bag, and the roller pump is activated. The inlet side of the bag is kept open to allow the perfusionist to monitor the volume in the left ventricle and to regulate pump speed accordingly (see text for explanation).

Comment

The physiologic justifications for employing a left ventricular vent are well known. Venting prevents left ventricular distention, decreases wall tension, eliminates isovolumic systolic pressure work, and improves subendocardial coronary flow [2–6]. It also helps create a dry field for distal coronary anastomoses. Previous studies have shown that using a vent improves cardiac performance immediately after coronary artery bypass operations [1]. Yet, the advisability of venting remains controversial. The major argument against venting is that the risk of an air embolus and the complexity of the vent system outweigh any physiologic or practical advantages.

Our method of left ventricular venting allows the perfusionist to monitor left ventricular distention and to apply appropriate countermeasures while minimizing the risk of "sucking air." There are no valves, needles, or other openings in the vent circuit that could allow air to enter the heart. The pledgeted triangular stitch around the vent improves the seal and therefore reduces the risk of air being sucked around the vent. Air can still be sucked back into the aorta through the open coronary artery during a distal anastomosis [7] unless the coronary artery is completely occluded. This can be avoided by asking the perfusionist to clamp the vent whenever the opened coronary artery is found to be totally dry. Priming the circuit with saline solution before connecting it to the vent allows the siphon to be established initially without using the roller pump to suck directly on the heart, again reducing the chance of sucking air. Also, because the initial priming of the circuit is done from the surgical field, the chance of causing air embolism by inadvertent reversal of the vent tubing is eliminated. This has been reported to be a common pump accident [8].

This venting system is cost efficient. There is no cost for the reservoir bag, and the tubing is inexpensive and easy to incorporate into any extracorporeal system. There are no special relief valves or elaborate tubing systems that increase complexity and cost. In addition, the vent can be replaced with a left atrial catheter at the conclusion of cardiopulmonary bypass, thus providing continuous measurement of left atrial pressure in the postoperative period. The left atrial line obviates the need for expensive Swan-Ganz catheters in uncomplicated cases [9].

In summary, we have described a simple, closed system for venting that allows the perfusionist to monitor left ventricular distention and to titrate the vent suction, thus reducing the chance of sucking air. Distracting conversations about the level of vent suction are minimized. Of course, this or any other left ventricular venting system cannot completely eliminate the possibility of introducing air into the heart. Constant diligence must be maintained by the surgeon and the perfusionist. We have used this method in more than 4,000 coronary artery bypass operations over the last 7 years and found it to be simple, effective, safe, and economical.

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Conjoined Subrectus Pocket for Permanent Pacemaker Placement in the Neonate

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We present a method of pacemaker implantation in neonates using a subxyphoid epicardial lead and subrectus placement of the pulse generator. This method is simple and safe and carries minimal morbidity.

(Ann Thorac Surg 1992;53:1130–1)

Permanent pacemaker placement has been shown to be an effective treatment for congenital heart block [1–4], yet it presents a challenge to the surgeon because of discrepancies in size between the patient and the hardware. In larger children, several methods have been employed for lead placement, including either an endocardial transvenous approach [1, 2, 4] or epicardial placement through a thoracotomy [2], sternotomy [3], or subxyphoid incision [4, 5]. The pulse generator has been placed in the intraperitoneal [3, 4], retroperitoneal [2], or intrapleural spaces [4], or in an infraclavicular subcutaneous or subpectoral pocket [1]. For the neonate, we have used a subxyphoid incision for epicardial lead placement and created a conjoined bilateral subrectus pocket, using a method similar to that described by DeLeon and colleagues for older children [5].

Technique

An upper midline incision is made in the epigastrium and carried down to the linea alba. The anterior rectus sheath is dissected from the subcutaneous tissues for a few millimeters bilaterally. The linea alba is incised, the xyphoid is freed and retracted, and the pericardium is exposed through the preperitoneal space. A transverse incision is made in the anterior pericardium, and stay sutures are placed for retraction both superiorly and inferiorly. 5-0 polypropylene anchoring sutures for the lead are placed on the anterior surface of the right ventricle but not tied, care being taken to avoid the coronary arteries. A "fishhook" epicardial lead (Medtronic model 4951-35; Medtronic, Inc, Minneapolis, MN) is then inserted securely into but not through the ventricular musculature. After appropriate lead parameters are obtained, the anchoring sutures are secured (Fig 1). The pericardium is closed with interrupted sutures.

The anterior and posterior rectus sheaths are separated bilaterally where they fuse to form the linea alba. In practice, we find this easier to perform after the linea alba has been incised in the midline. After initial sharp dissection, the rectus musculature is easily bluntly elevated from the posterior rectus sheath to the linea semilunaris bilaterally. The posterior sheaths are reapproximated in the midline with running 3-0 polyglycolic acid sutures to create a conjoined rectus pocket (Fig 2).

The lead is connected to the pulse generator (Medtronic Minix, model 8341, Medtronic, Inc), which is placed within the subrectus pocket, posterior to the musculature. Excessive lead is coiled and placed posterior to the generator (Fig 3). The anterior rectus fascia is reapproximated, and the subcutaneous tissues and skin are closed.

Comment

We find epicardial lead placement to be the optimal approach in neonates. Transvenous endocardial lead placement has been advocated in the neonate, but experience has been limited to 1 published case [1]. This baby experienced a possible venous air embolism as well as excessive blood loss, leading to a further compromised hemodynamic state. Whether endocardial leads have better long-term function and lower chronic thresholds is controversial [1, 4, 6]. Although there are some indications that suture-type epicardial leads exhibit lower chronic thresholds than the fishhook lead that we have employed, this has not been a problem in our experience [6]. Although coiling of the lead in the right atrium to allow for subsequent growth makes endocardial lead placement clearly possible in young children, the small size of the heart makes this difficult in the neonate. In addition, the distance between the heart, a subclavian entry site, and an abdominal generator pocket requires that a lot of lead slack will be consumed for a given amount of growth. There is also the risk of perforation of the thin-walled neonatal right ventricle with endocardial lead placement.

The subxyphoid approach allows for excellent visualization of the anterior myocardium in the newborn and avoids a thoracotomy. Because the cardiac mass is situated more caudally in the newborn than in the adult, the right ventricular surface can be exposed without undue traction on the sternum or resection of the xyphoid.

Placement of the pulse generator in a conjoined rectus sheath pocket allows easy access with minimal morbidity. Others have positioned the pulse generator within the abdomen [3, 4] or thorax [4], or in the retroperitoneal space [2], which makes external programming difficult [4].

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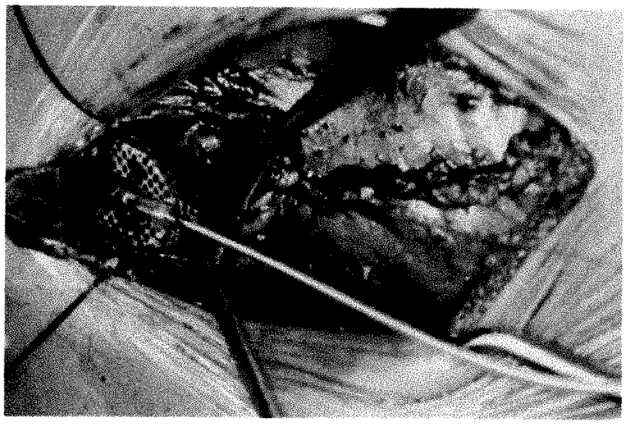

Fig 1. Surgeon's view of the epicardial lead positioned in the right ventricle. The posterior rectus sheath has been reapproximated. (Surgeon's view rotated 90 degrees clockwise.)

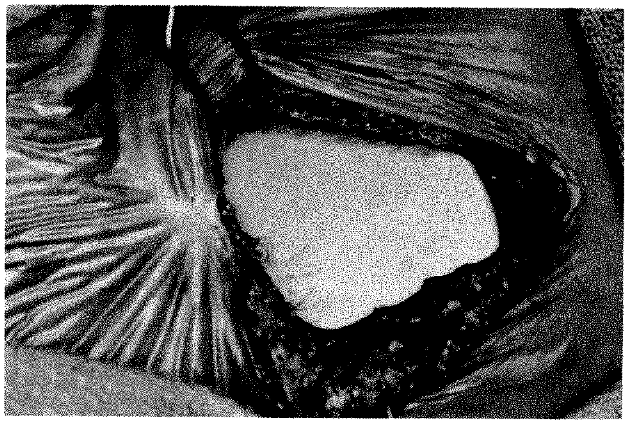

Fig 3. The pulse generator has been positioned within the subrectus pocket. (Surgeon's view rotated 90 degrees clockwise.)

Also, if replacement of the generator is required, the operative approach is far more complicated under such circumstances. Subcutaneous positioning in the neonate frequently results in skin ischemia. Placement of the pulse generator between the rectus muscle and the posterior rectus sheath allows the generator to be analyzed and programmed while protecting the overlying skin from pressure necrosis. Generator change for battery fatigue should require only reincision of the midline. Alternatively, a new endocardial lead can be placed, because the child will have grown much larger by the time replacement is required.

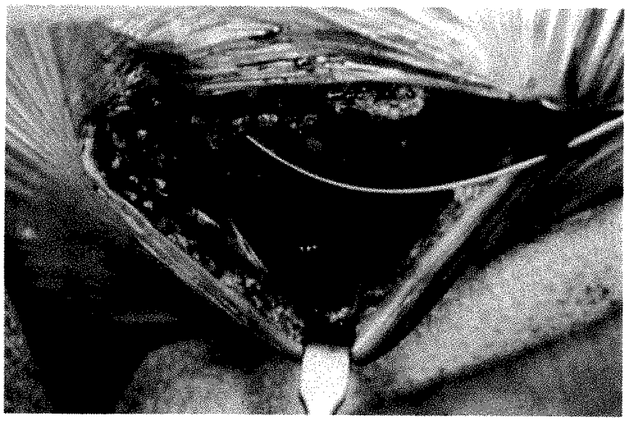

Fig 2. The pericardium has been closed and the rectus abdominis musculature elevated from the posterior rectus sheath. (Surgeon's view rotated 90 degrees clockwise.)

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Surgical Treatment of Tricuspid Regurgitation

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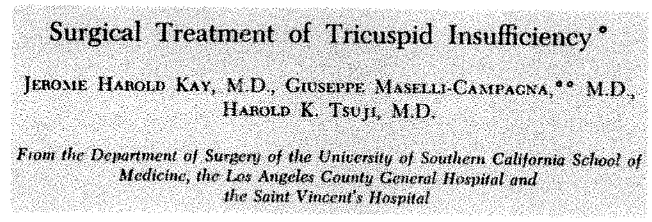
The technique of tricuspid valve repair for tricuspid regurgitation has been used effectively since 1961. The first publication of the method appeared in 1965 in the *Annals of Surgery*. The procedure has changed little since that time and has afforded excellent long-term results. The procedure consists of excluding the annulus of the posterior leaflet of the tricuspid valve. The technique is simple, fast, hemodynamically effective, and durable. It carries no risk of heart block because the posterior leaflet annulus is far from the conduction system. An inferior caval snare may produce inadequate drainage with resulting increased back pressure on the liver leading to hepatocellular necrosis and lethal postoperative liver dysfunction in 3 to 5 days. Therefore, an inferior caval snare is never used when repairing or replacing the tricuspid valve for acquired or rheumatic heart disease. Morbidity and mortality are also decreased by restricting fluids in the postoperative period.

(Ann Thorac Surg 1992;53:1132–3)



Surgical Treatment of Tricuspid Insufficiency*

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In the late 1950s and early 1960s, we were repairing mitral valves for pure mitral regurgitation or mitral stenosis and mitral regurgitation. In the vast majority of patients with tricuspid regurgitation, the regurgitation was secondary to mitral valve disease with gross tricuspid annular dilatation. Because it was easier to make a two-leaflet valve competent than a three-leaflet valve, the annulus was narrowed in such a fashion to produce a two-leaflet valve. This was and still is accomplished by placing two or three thick silk sutures in the annulus to obliterate the annulus of the posterior leaflet (Fig 1). Because of the position of the conduction bundles, the technique carried no risk of producing heart block. The technique was effective, simple, and fast, and in the early days of open heart surgery, the results of the procedure were predictably good and saved time on cardiopulmonary bypass [1]. Even with improvement with the heart-lung machines and safety of bypass, there were still deaths in very ill patients.

The majority of deaths in these ill patients with long-standing tricuspid regurgitation occurred within the first week or two after operation. Death was due to liver necrosis or pulmonary failure. The patients who died of liver failure had long-standing cirrhosis. These patients appeared well at first, but after a few days progressive jaundice developed and they died. At autopsy marked cirrhosis of the liver and necrosis of the few remaining liver cells were found. What was the reason for necrosis of the remaining normal liver cells after cardiopulmonary bypass? We reasoned that during open heart operation with an inferior caval catheter in place and a tie snugged around the inferior vena cava, drainage through the inferior caval catheter might not always be adequate, thereby producing an increase in pressure in the inferior vena cava. This increased pressure would be reflected back into the cirrhotic liver, with pressure on the few normal remaining functioning liver cells against the scarred latticework, causing destruction of the functioning liver cells. This does not occur during cardiopulmonary bypass in patients with a normal or near-normal liver. For this reason, since the early 1960s, superior and inferior caval ties have not been employed for any patients undergoing mitral valve operations. If the tricuspid valve is to be repaired or replaced, only a superior vena caval tie is used. With this modification there was a significant decrease in mortality [2].

During the late 1950s the survival of patients with congenital heart defects with high pulmonary artery pressure after correction of the defect was improved by limiting fluid in the postoperative period. In the patients with long-standing mitral valve disease with or without tricuspid regurgitation, fluid restriction was also important for lowering morbidity and mortality.

It was also noted that patients with serious mitral valve disease in whom a transvenous pacemaker had previously been inserted may have concomitant tricuspid regurgitation. At the time of mitral replacement or repair, the pacemaker lead is excluded in suturing the annulus of the area of the posterior leaflet, thereby correcting the regurgitation produced by the pacemaker lead.

Our research with tricuspid valve replacement in animals in 1974 further reinforced our concern with tricuspid valve replacement. Besides problems with thromboses and emboli in the tricuspid area, mechanical prosthesis have problems because the metal leaflets or poppets may get caught on the surrounding musculature of the right ventricle. In the experimental studies in calves comparing

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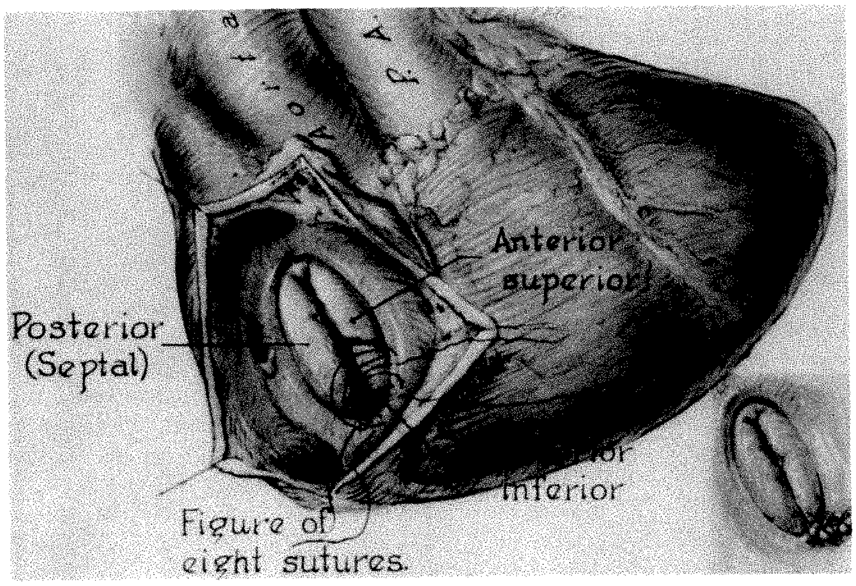

Fig 1. Method of correcting tricuspid insufficiency. Figure-of-eight sutures of 0 silk are taken in the annulus of the anterior inferior leaflet beginning at the juncture of the posterior and anterior inferior leaflet. Annulus of the posterior leaflet is preserved. (Reproduced with permission from Kay JH, Maselli-Campagna G, Tsuji H. Surgical treatment of tricuspid insufficiency. Ann Surg 1965;162:53–8.)

ball valves, disc valves, and disc valves with a muscle guard, the outflow areas of the prostheses were narrowed most significantly with the ball valves and disc valves without a muscle guard. The muscle guard protected the valve poppet from being encroached upon by the muscle of the right ventricle [3]. Our concern regarding tricuspid valve replacement was confirmed with this research work.

The technique for repairing the tricuspid valve has not varied in the past 30 years and consists of obliterating the posterior annulus with two or three thick silk mattress sutures over Teflon felt. The method of repairing the tricuspid valve has stood the test of time. It is easy to perform and is durable. If the mitral valve is repaired rather than replaced and sinus rhythm is present, long-term anticoagulation with its morbidity and mortality is not required.

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Asymptomatic Bronchogenic Cysts: What Is the Best Management?

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The management of patients with uncomplicated bronchogenic cysts has evolved over the last decade with the development of more precise diagnostic techniques and a better understanding of the variable natural history of these lesions. Although an aggressive surgical approach is still indicated for infants and children, it is acceptable to treat asymptomatic bronchogenic cysts in adults in a conservative manner. Observation alone may be indicated for small, classic, asymptomatic cysts. The use of mediastinoscopy or percutaneous or transbronchial needle techniques for carinal or paratracheal cysts offers the option of fluid aspiration or wall biopsy, thus avoiding thoracotomy. An air-fluid level in the cyst, the presence of malignant cells in the aspirate or biopsy, the development of symptoms, or enlargement or recurrence of the cyst on follow-up examination mandates complete surgical removal at thoracotomy. This is also indicated for intraparenchymal bronchogenic cysts, which are more prone to bronchial communication and infectious complications and for which the distinction from a carcinoma with a cystic component may be difficult.

(Ann Thorac Surg 1992;53:1134–7)

Bartholinus [1] published the first account of a congenital lung cyst in 1687, and Meyer [2] first described a case of bronchogenic cyst in 1859. Koontz [3] published the first case report in the American literature in 1925. The first successful surgical management of such cysts was by Swanson and associates [4] in 1928, who used aspiration and sclerosis with formaldehyde and Dakin's solution to ablate the cavity. This technique did not have consistent success, leading many surgeons [5–7] to adopt a more aggressive surgical approach. Controversy continues as to the best management of asymptomatic bronchogenic cysts, especially in adults.

Embryology and Histology

Bronchogenic cysts are an anomaly of bronchial development from the primitive ventral foregut. They arise from cells that are isolated from the main pulmonary branching when the lung bud separates from the primitive gut [8–11]. These cysts usually arise in proximity to the trachea, major bronchi, or esophagus, more often on the right side, with a male predominance [8, 9, 12]. They may be found within the pulmonary parenchyma in 25% of patients [12]. Intrapericardial bronchogenic cysts have been reported [13]. Although bronchogenic cysts are usually located above the diaphragm, rare reports [14] of isolated subdiaphragmatic bronchogenic cysts have appeared.

Bronchogenic cysts are usually spherical and as large as 10 cm in diameter. Most often they are unilocular rather than multilocular, although they may contain internal trabeculations. The cysts are usually thin walled and tend to conform to the anatomic space in which they arise. On histologic examination, they may contain some normal bronchial elements, ie, smooth muscle, elastic tissue, fibrous tissue, and cartilage [8, 10, 12, 14–16]. The cyst is filled with mucoid material, which may be clear, white, turbid, or blood tinged, and is usually lined with pseudostratified ciliated columnar epithelium. Squamous metaplasia may be present [10].

Prevalence and Clinical Features

Bronchogenic cysts are relatively uncommon congenital lesions with prevalences of 1:42,000 and 1:68,000 admissions in two hospital series [14]. In a review of 13 series comprising 2,163 patients with mediastinal lesions, the prevalence of bronchogenic cyst was 6% [17].

Most bronchogenic cysts cause few, if any, symptoms in adults. Symptomatic cysts are most often seen in children. Respiratory insufficiency and even death in neonates or infants may result from distortion of the more compliant and compressible airways by the cyst [18–20]. Bronchial cysts should always be considered in the differential diagnosis of congenital stridor [8, 14, 21, 22].

Although bronchogenic cysts can be asymptomatic for years, some authors believe that many such cysts will eventually cause symptoms from compression of surrounding structures or infection. These symptoms include chest pain, dysphagia, dyspnea, and cough [10, 12, 23]. Infection is the most common serious complication in adults, with a 33% incidence as reported by Sirivella and colleagues [21].

Mediastinal bronchogenic cysts rarely communicate

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with the tracheobronchial tree [12]; when they do, symptoms such as cough, fever, sputum production, and hemoptysis are frequently present [8, 24, 25]. Roentgenography of the chest may show an air-fluid level [8]. Intraparenchymal cysts are more likely to have a connection to the tracheobronchial tree and are thus more prone to infectious complications [10, 12].

In the absence of infection, symptoms depend on the location and size of the cyst [16]. In addition to chest pain and symptoms from compression of the tracheobronchial tree or esophagus, other manifestations include cardiac arrhythmias with left atrial compression [26], auscultatory findings of mitral stenosis secondary to pericardial compression [27], superior vena cava syndrome [28–30], and pulmonary artery stenosis [29].

Potentially the most serious but fortunately rare complication of bronchogenic cysts is malignant degeneration [31–47]. In 1941, Womack and Graham [38] first described abnormal cellular growth in the lining of congenital lung cysts represented by squamous metaplasia, but they believed it was not justified to consider this change malignant clinically. Moersch and Clagett [32] asserted in 1947, however, that bronchogenic cysts are lined by a type of mucosa that may lend itself to the development of carcinoma.

In a recent comprehensive review of mediastinal pathology, Marchevsky and Kaneko [39] stated that "malignant transformation of the epithelial components of a bronchogenic cyst has not been described." Numerous reports [31–47] suggesting the possibility of malignant degeneration have been published, but in many of these cases the precise relationship of the malignancy to the cyst is unclear. Bronchogenic cysts are characterized by their lining, and some reports [32–35, 40] suggesting malignant degeneration do not adequately document the fact that the cyst is indeed a congenital bronchogenic cyst as opposed to an acquired cyst. At times it is difficult to distinguish between carcinoma with cavitation and a bronchogenic cyst in which carcinoma develops.

Only a few case reports in the English-language literature [31, 41–43] give reasonable suspicion that a malignancy may have arisen from a congenital bronchogenic cyst in adults. These cases include one bronchial adenoma of the carcinoid type [43], one anaplastic carcinoma [41], one squamous cell carcinoma [31], and one leiomyosarcoma [42]. Because of inadequate documentation, the remainder of the reports allow some doubt as to the type of cyst or origin of the tumor. Three cases in the pediatric population have been reported that suggest that malignant degeneration of congenital bronchogenic cysts may be a rare occurrence in children [36, 46, 47].

Most contemporary reviews [12, 17, 39] conclude that the risk of malignancy in congenital bronchogenic cysts is minute and that the risk of other associated complications is of greater concern. A cystic component within a carcinoma of the lung is much more likely than the risk of malignant degeneration of a congenital bronchogenic cyst.

Diagnosis

Bronchogenic cysts are usually discovered incidentally on routine roentgenography of the chest as a smooth oval or round homogeneous density in close proximity to the major airways [8, 12]. They are somewhat more common in the subcarinal and right hilar areas [48]. Maier's [16] classification, based on location, includes paratracheal, carinal, hilar, paraesophageal, and miscellaneous. The hilar group was most common in Maier's series, although other authors [25] state that carinal bronchogenic cysts are the most frequently reported of the benign congenital mediastinal cysts.

Roentgenography of the chest in the posteroanterior and lateral projections often suggests the diagnosis of bronchogenic cyst, and computed tomography confirms its cystic nature (low Hounsfield units) and demonstrates its relationship to the tracheobronchial tree or esophagus [11, 24, 49]. Occasionally, turbid fluid within the cyst may result in higher Hounsfield numbers [50]. In infants, the diagnosis may not be as evident on simple roentgenography of the chest because a mass is not immediately apparent in more than 50%. Uncommonly, a barium swallow may be helpful by suggesting esophageal compression by the cyst [20]. Neither esophagography nor bronchography is useful in adults except to confirm esophageal or airway compression. Needle aspiration, however, may confirm the diagnosis [48].

Treatment

The options currently available for the treatment of patients with bronchogenic cysts include observation, fine needle aspiration, mediastinoscopy for aspiration and biopsy, thoracoscopy, and thoracotomy or mediastinoscopy for resection.

The possibility of malignant degeneration, future symptoms, and recurrence after aspiration has led many surgeons [8, 12, 14, 17, 21, 23, 29, 31, 35, 51] to advocate complete removal by thoracotomy in all patients. For cysts in the most common subcarinal location, the procedure is accomplished through a right posterolateral thoracotomy. When thoracotomy is undertaken for removal of a cyst, every effort should be made to remove the entire cyst to prevent recurrence [29]. When the cyst cannot be removed completely at thoracotomy, partial excision with deepithelialization may be an alternative [52].

The rationale for such an aggressive approach is the substantial proportion of patients in surgical series in whom serious complications develop. However, long-term follow-up data on patients with incidentally discovered asymptomatic cysts are not readily available, and surgical series may be skewed by symptomatic patients. The incidence of subsequent symptoms in initially asymptomatic patients with bronchogenic cysts is not known.

With the improved diagnostic accuracy of computed tomography and the recognition that some bronchogenic cysts remain asymptomatic throughout their natural history, some authors [53, 54] now advise operation in adults only for suspected malignancy and for symptoms such as infection, tracheobronchial compression, or enlargement.

All cysts in children should probably be removed because the cysts do not spontaneously regress, and they occupy space needed for the development of normal respiratory tissue [24, 54, 55].

For adult patients, Ginsberg and colleagues [24, 54] propose that small asymptomatic cysts may be followed up with periodic roentgenography of the chest, whereas enlarging or symptomatic cysts should be removed. They acknowledge the rare possibility of malignant degeneration. Kirschner [56] reported on 3 patients who were observed after mediastinoscopic or needle aspiration with no enlargement or symptoms at 8, 10, and 15 years.

Transbronchial needle aspiration may be used for both diagnosis and treatment of mediastinal bronchogenic cysts in adults, realizing that repeated aspiration from more than one site may be necessary for trabeculated cavities [24, 48, 57]. This may be particularly applicable to subcarinal cysts.

Carlens [58] originally described the aspiration and biopsy of a cystic mediastinal mass using mediastinoscopy. Subsequent treatment of bronchogenic cysts through the mediastinoscope, either by aspiration and wall biopsy or by complete removal, has been reported by Pursel and colleagues [59] and Ginsberg and colleagues [54]. The instillation of sclerosing agents, such as tetracycline or hypertonic saline solution, into the cyst may destroy the lining cells and thereby decrease the chance of recurrence [24].

Mediastinoscopy cannot be used for anterior or posterior mediastinal cysts but only for cysts adjacent to the proximal tracheobronchial tree. This technique should *not* be used when an air-fluid level suggesting a tracheobronchial communication is present. It has been reported [24] that about 50% of bronchogenic cysts have been treated successfully by mediastinoscopy, eliminating the need for thoracotomy. Biopsy of the cyst and close follow-up studies are necessary if this treatment option is chosen.

Rodgers and associates [11] have reported removal of an extralobar bronchogenic cyst using a thoracoscope. This technique may be applied more widely as experience grows with a new generation of instrumentation.

Comment

After the diagnosis of bronchogenic cyst has been established, the decision concerning surgical removal of the cyst may be difficult, especially in an asymptomatic patient. Based on a review of the literature, it may be acceptable to approach the diagnosis and treatment of suspected bronchogenic cysts in adults in a conservative manner. The use of transbronchial needle aspiration, mediastinoscopy, or thoracoscopy for carinal or paratracheal cysts permits decompression of the cyst and examination of its contents for evidence of malignancy. An air-fluid level suggesting tracheobronchial communication, the presence of malignancy, or the development of symptomatic recurrence or enlargement on follow-up study mandates complete surgical removal of the cyst at thoracotomy. Because of their higher incidence of complications [10], presumed intrapulmonary bronchogenic cysts should usually be removed. Any cystic lesion that does not have the classic roentgenographic appearance or location of a mediastinal bronchogenic cyst, especially those that are intraparenchymal, should be removed surgically to exclude the possibility of malignancy or infectious lesion.

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Practice Guidelines in Cardiothoracic Surgery

During the last 10 years, members of our specialty have been fielding, on an individual and on a collective basis, requests regarding standards of care as they relate to our patients. These requests have come mainly from third-party payors on a national level, as well as private carriers, and also from medicolegal committees within our specialty organizations. The Council of The Society of Thoracic Surgeons, after much deliberation involving many council meetings, ultimately decided that these requests were legitimate and that a carefully structured response from our specialty was indeed indicated. From the outset, it was decided that these documents should represent the opinions of our specialty as completely as possible and, therefore, the active participation and support of the other three major thoracic societies (the American Association for Thoracic Surgery, the Western Thoracic Surgical Association, and the Southern Thoracic Surgical Association) have been solicited.

The committee and subcommittees formed as a result of this action of the Council of The Society of Thoracic Surgeons have met on many occasions and have had considerable deliberations concerning these matters. First of all, a title for these documents was thoroughly discussed; the use of the word "guidelines" seemed most appropriate and perhaps "minimal guidelines" would be even more appropriate. There was a clear understanding among the participants that this was not to be an effort to provide a textbook description of each procedure with a detailed analysis of every facet of patient care and outcome analysis, but rather it was to be a simple description of those things that are normally anticipated in developing the indications for surgery, as well as simple statements regarding those things to be anticipated before, during, and after the operative procedure in the care of the patient. It also was agreed that an attempt would be made to provide some broad-range outcome statements. It was also understood that, even though this work product could be entitled "minimal guidelines," some of the items identified might not be included in the care of an individual patient. Further, it was clearly understood that many other items might logically and appropriately be included in patient care and not included in these minimal guidelines.

Finally, and perhaps most importantly, it was agreed upon that this work product should be a "living document" and that frequent review and revision would be a part of the work intended. With the rapid advance of technology and patient care techniques, this final point is essential. Because of the volume of this effort, it will not be published in total form, but rather in the various elements of our specialty as the work product is completed and publication is appropriate. Because of the nature of the presentation of this material to thoracic and cardiovascular surgeons, it is clearly understood that revision of the first published portions of these documents may well be indicated prior to completion of the coverage of our specialty. Because of this, comments and suggestions regarding these guidelines are encouraged and solicited and should be addressed to the management of The Society of Thoracic Surgeons. It is our commitment to act upon these comments and suggestions and to revise and maintain this living document in a timely fashion.

George G. Lindesmith, MD
President, The Society of Thoracic Surgeons
1988–1989

Background

During his tenure as President of The Society of Thoracic Surgeons, George G. Lindesmith appointed the Ad Hoc Committee for Cardiothoracic Surgical Practice Guidelines. The current committee composition is as follows:

GEORGE C. KAISER, MD, CHAIRMAN, St. Louis
THOMAS D. BARTLEY, Pueblo, CO
JOSEPH S. COSELLI, Houston
JAMES A. DEWEESE, Rochester, NY
T. BRUCE FERGUSON, JR, St. Louis
THOMAS B. FERGUSON, St. Louis
RICHARD G. FOSBURG, La Jolla
ROBERT H. JONES, Durham
GEORGE G. LINDESMITH, Los Angeles
KEITH S. NAUNHEIM, St. Louis
D. GLENN PENNINGTON, St. Louis
MARVIN POMERANTZ, Denver
W. GERALD RAINER, Denver
ROBERT M. VANECKO, Chicago
ANDRES S. WECHSLER, Richmond

The organizational meeting of the Committee was held in Boston, Massachusetts, on May 8, 1989. During this and subsequent meetings, the guideline format and its degree of complexity were discussed extensively. It was recognized that practice guidelines were being constructed by many organizations, each with its own agenda and requirements. Therefore, guidelines varied in detail and complexity according to the perceived needs of the constituency. Furthermore, it was noted that there are no universally accepted guidelines for writing practice guidelines. However, to help the STS committee formulate its plan, guidelines already in existence or being developed were collected from other medical and peer review organizations, third-party payors, and both federal and state governments. This information was invaluable in assisting the Committee in arriving at its decisions regarding the structure and complexity of cardiothoracic surgical practice guidelines. After careful and extensive deliberation, it was decided to approach Practice Guidelines under the following rubrics:

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1. **The guidelines would be procedure-oriented.** Appropriate CPT codes were to be indicated. This would allow appropriate identification of each procedure as it would be coded in the revised CPT-4 code book. The Society's CPT-4 Advisory Committee, under the Chairmanship of Sidney Levitsky, was assisting in the revision of the cardiothoracic surgical codes which in many instances were out of date or in which codes were entirely lacking for procedures such as thoracic organ transplantation and left ventricular assist device insertion. Furthermore, listing of the procedure and diagnostic codes would assist members in their practice and other bodies in identifying the exact procedure being performed.
2. **The field of cardiothoracic surgery would be divided anatomically and associated pathologic processes in each area would be addressed.** Although the guidelines were to be procedure oriented, the field of cardiothoracic surgery was organized along anatomic and pathologic lines. Organization of the guidelines in this manner was decided upon to allow ease of categorization and implementation. This apparent ambivalence was accepted to facilitate guideline development, yet encompass the entire field of cardiothoracic surgery. Although some organizations that developed practice guidelines had struggled with this apparent dichotomy between disease entities and procedures, the Committee felt its approach was practical and would expedite this complex process.
3. **The criteria published by the American College of Obstetricians and Gynecologists* would be used as the model for the outline of the areas to be addressed for each Practice Guideline.** Their outline is:

    Procedure
    Indication
    Confirmation of Indication
    Action Prior to Procedure
    Contraindications

    Additions were made to this outline to address aspects not included in that outline and to make it more compatible with our needs. The subsequent headings decided upon by the Committee were:

    Diagnosis
    Procedure
    Indication
    Confirmation of Indication
    Relative Contraindications
    Actions Prior to Procedure
    Actions During Procedure
    Actions Following Procedure
    Outcome
    References

It was decided that cardiothoracic surgical textbooks would be the references of choice. There were many reasons for this decision, not the least of which was that these would represent the generally accepted view in the cardiothoracic surgical community, and only a few references would be required, thereby avoiding extensive and cumbersome bibliographies. For newer procedures for which textbook references were incomplete or unavailable, it was agreed that appropriate references from the cardiothoracic surgical literature would be supplied.

In view of the increasing emphasis by many upon outcome, it was agreed to include some estimate of expected outcome for each procedure.

Subcommittees for each cardiothoracic surgical category were appointed with a member of the Ad Hoc Committee as chairman of the subcommittee. These subcommittees and their membership are as follows:

1. Ischemic Heart Disease

    ROBERT H. JONES, CHAIRMAN
    GERALD M. LAWRIE
    WEI-I LI
    BRUCE W. LYTLE

2. Valvular Heart Disease

    THOMAS D. BARTLEY, CHAIRMAN
    JOSEPH M. CRAVER
    ROBERT A. GUYTON

3. Thoracic Aortic Disease

    JOSEPH S. COSELLI, CHAIRMAN
    E. STANLEY CRAWFORD
    RANDALL B. GRIEPP
    NICHOLAS T. KOUCHOUKOS
    D. CRAIG MILLER

4. Chest Wall, Diaphragm, Mediastinum, Pericardium

    THOMAS B. FERGUSON, CHAIRMAN
    LARRY R. KAISER
    KEITH S. NAUNHEIM
    CHARLES L. ROPER
    WILLIAM F. SASSER

5. Esophageal Disease

    ROBERT M. VANECKO, CHAIRMAN
    ROBERT J. GINSBERG
    ALEX G. LITTLE
    MARK B. ORRINGER

6. Bronchopulmonary Disease

    RICHARD G. FOSBURG, CHAIRMAN
    JOHN R. BENFIELD
    RICHARD M. PETERS
    THOMAS W. SHIELDS

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* Quality Assurance in Obstetrics and Gynecology, 1988 Edition, The American College of Obstetricians and Gynecologists, 409 12th St SW, Washington, DC 20024-2188.

7. Transplantation (heart, lung, heart-lung) and Heart Assist Devices

D. GLENN PENNINGTON, CHAIRMAN
WILLIAM A. BAUMGARTNER
A. MICHAEL BORKON
JACK J. CURTIS
VERDI J. DiSESA
J. KENT TRINKLE

8. Electrical Problems (pacemakers, arrhythmias, AICD)

MARVIN POMERANTZ, CO-CHAIRMAN
W. GERALD RAINER, CO-CHAIRMAN

9. Congenital Heart Disease

GEORGE G. LINDESMITH, CHAIRMAN
JEFFREY M. DUNN
HILLEL LAKS
WINFIELD J. WELLS

James A. DeWeese, MD, serves as liaison between the cardiothoracic surgical organizations and the vascular surgical organizations, the North American Chapter of the International Cardiovascular Society, and the Society for Vascular Surgery. These vascular surgical organizations are developing practice guidelines for vascular surgery. This method of cooperation has been adopted to avoid reduplication of effort.

Each subcommittee was charged with the development of guidelines for that category of cardiothoracic surgical practice. In rare instances a procedure might be potentially addressed by more than one subcommittee. Any possibility for overlap was resolved by the parent committee. As an initial effort, each subcommittee was requested to develop guidelines for three of the most commonly performed procedures in its area of expertise. These practice guidelines were then reviewed and critiqued by the entire Ad Hoc Committee and all subcommittees. After refinement, the final results were submitted to the Council of The Society of Thoracic Surgeons for approval. It was anticipated that this complex ratification process might develop snags. Therefore initially, the introductory, preoperative evaluation, and institutional requirement sections along with guidelines for nine procedures were submitted for approval. It was anticipated that any potential problems with this review process that arose could then be resolved making ratification of future guidelines easier. Because in any extensive and complex review process as outlined there might be some differences of opinion, it was proposed that the Council of The Society of Thoracic Surgeons would be the final arbiter. The goal of this review process is to achieve consensus, but at the same time recognize that practice guideline development is, and always will be, a dynamic process.

It was decided that the first iteration of the guidelines be published every few months in *The Annals of Thoracic Surgery*. On the following pages are the first set of practice guidelines and the introductory, preoperative evaluation, and institution requirement sections. It is anticipated that eventually guidelines covering the entire specialty will be collated and published as a separate document. It should be emphasized that one of the most important aspects of this process is that these guidelines will require continual modification and revision as clinical cardiothoracic surgical practice changes.

I would like to thank the members of the Ad Hoc Committee and of each subcommittee for their effort and excellent cooperation.

George C. Kaiser, MD
Chairman, Ad Hoc Committee for Cardiothoracic Surgical Practice Guidelines

Introduction

The following sections provide basic practice guidelines for those individuals qualified in the specialty of cardiothoracic surgery. Although the practice of medicine requires a strong scientific foundation, medicine is also an art requiring both intuitive skills and good judgment. Occasionally, objective decisions concerning patient management must be modified depending upon such factors as individual patient characteristics or other associated factors. Such cognitive functions are an integral and essential part of the practice of cardiothoracic surgery with regard to preoperative patient evaluation, selection of operative procedures, and postoperative patient care until the patient has recovered. The ability to modify the process as needed for the greater benefit of the patient is vital if an optimal outcome is to be achieved for each patient. These intuitive and cognitive skills are essential to the successful practice of cardiothoracic surgery and must be applied in every phase, frequently requiring modification of the patient's care from preoperative preparation to discharge planning. These intellectual abilities are developed, sharpened, and maintained by constant exposure to patients in a clinical setting. In addition, the practitioner must update his or her fund of scientific information by journal review, attendance at scientific meetings and postgraduate seminars, as well as by consultation with colleagues both inside and outside of the specialty of cardiothoracic surgery.

Because guidelines are but one aspect in the ever-evolving field of cardiothoracic surgery, it is anticipated that these guidelines must be modified frequently to keep pace with the advances. As a background upon which practice guidelines will be developed, it is pertinent to delineate the extent of expertise encompassed by the specialty of cardiothoracic surgery. This has already been done.

Scope of Thoracic Surgery[†]

The thorax or chest extends from the neck to the abdomen and contains the principal organs of the circulatory and respiratory and upper gastrointestinal systems. The specialty of thoracic surgery consists of the diagnosis and

treatment of the major organs comprising the thorax, but is not totally confined to this area. More precisely, it includes the surgical treatment of congenital anomalies, malfunctions, diseases, and injuries of the thoracic cage, the heart and great vessels, the tracheobronchial system and lungs, esophagus, diaphragm, other mediastinal contents, and circulatory systems in all age groups.

[†] Modified from "Guidelines for Hospital Privileges for Thoracic Surgeons," developed by The Society of Thoracic Surgeons, endorsed by The American Association for Thoracic Surgery in 1986, and revised in 1991 and 1992. Copies may be obtained from: The American Association for Thoracic Surgery, Thirteen Elm St, Manchester, MA 01944; or The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611-4267.

This specialty is recognized by certification by the American Board of Thoracic Surgery or fellowship in cardiovascular and thoracic surgery in the Royal College of Surgeons of Canada, or certification of special competence in general thoracic surgery by the Royal College of Surgeons of Canada. Certification requires specific training in an approved residency program which educates its students in both the diagnosis and treatment of diseases, malfunctions, and injuries of the thoracic cavity and its contents. This requires a detailed knowledge of normal and abnormal anatomy and physiology within the cardiorespiratory and gastrointestinal systems. Specific technical and cognitive skills must be learned both in the operating theater and in the post surgical setting which allow for excision, repair or replacement (via tissue transplant or prosthesis) of the contents of the thorax. These abilities must include detailed knowledge of and expertise with the operative techniques, the medications, and technological hardware required for the safe and expeditious performance of these procedures.

Fields of expertise practiced by thoracic surgeons include: 1) Benign and malignant tumors of the lung, chest wall, esophagus and stomach and mediastinal contents; 2) Coronary artery disease and its complications; 3) Diseases of the great vessels; 4) Valvular heart disease; 5) Electrophysiological arrhythmia ablation and pacemakers; 6) hernias and other pathology of the diaphragm; 7) Malfunctions of the esophagus; 8) Congenital and developmental anomalies of the cardiovascular system, diaphragm, esophagus, trachea and all structures within the chest; 9) Gastrointestinal endoscopy; 10) Bronchoscopy, thoracoscopy, and mediastinoscopy; 11) Peripheral vascular surgery as associated with major vessel disease; and 12) Blunt and sharp injuries to the thorax (trauma) including preoperative diagnosis, surgical evaluation, operative management and postoperative care.

An appropriately trained and credentialed thoracic surgeon should be expected to request privileges in those areas covered by his training. Training in Canadian programs is not in every case equivalent to that required by the ABTS. In those instances, the actual training received must be evaluated in the process of granting privileges. Those privileges may include, but not be limited to, the following list:

Thoracic and cardiovascular surgical privileges (for adults and children)
All operations involving resection, reconstruction, repair or biopsy of the lung and its parts (e.g. pneumonectomy, lobectomy, segmentectomy, localized resection, sleeve resection, in continuity with chest wall resection, including transplantation, etc., but not limited to these); and procedures incidental to the above.
All operations involving resection of the chest wall or the pleura, such as resection of chest wall tumor, pleurectomy, decortication, thoracoplasty, resection of first (or other) rib(s), empyema drainage, sternoplasty (for pectus excavatum or carinatum), etc., but not limited to these; and procedures incidental thereto.
All operations involving resection, reconstruction or repair of the trachea and bronchi, such as tracheostomy, tracheal resection, bronchotomy, bronchoplasty, etc., but not limited to these; and procedures incidental thereto.
All operations involving resection, reconstruction or repair of the esophagus and diaphragm, such as diverticulectomy, esophagectomy, esophagogastrectomy, colon interposition, jejunal interposition, hiatal herniorrhaphy, removal of diaphragmatic tumors, repair of the diaphragm, etc., but not limited to these; and procedures incidental thereto.
All operations of the pericardium, involving resection, reconstruction, drainage, etc., such as pericardiectomy or pericardiotomy, but not limited to these; and procedures incidental thereto.
All endoscopic procedures and instrumentations involving the esophagus and tracheobronchial tree, such as laryngoscopy, bronchoscopy, thoracoscopy, esophagoscopy, esophageal dilatation, etc., but not limited to these; and procedures incidental thereto.
Lymph node and superficial biopsy procedures, such as scalene or axillary node biopsy, subcutaneous and muscular biopsy etc., and procedures incidental thereto.
All procedures involving biopsy, excision of tumor, drainage, etc., of the mediastinum, such as mediastinoscopy or mediastinotomy, but not limited to these; and procedures incidental thereto.
Closed heart operations, both congenital and acquired (including reconstruction with grafts)
Open heart operations, both congenital and acquired (including valvuloplasty, replacement, reconstruction with grafts or transplantation)
Surgery of tumors of the heart and pericardium
Surgery of arrhythmias (arrhythmias ablation)
Surgery for implantation of artificial heart and mechanical devices to support or replace the heart partially or totally.
Correction or repair of all anomalies or injuries of great vessels and branches thereof, including aorta, pulmonary artery, pulmonary veins, venae cavae, but not limited to these; and procedures incidental thereto.
All operations for myocardial revascularization (endarterectomy, bypass grafts or internal mammary artery or other grafts to coronary arteries).
Operative procedures for correction or palliation of arteriosclerotic vessels, including the aorto-iliac-femoral system, but not limited to these; and procedures incidental thereto.
All operations for placement or replacement of cardiac pacemaker systems, including multi-chamber sensory pacemakers, automatic implantable defibrillators, whether epicardial or pervenous approach, but not limited to these; and procedures incidental thereto.
All operations involving transplantation of the heart, heart-lung block, and single or double lung transplants.

These guidelines have been developed by the Ad Hoc Committee for Cardiothoracic Surgical Practice Guidelines of The Society of Thoracic Surgeons. Numerous professional organizations have been involved in the development of the practice guidelines, and there is a diversity of opinion concerning their format and content. Because there are no established standards for writing practice guidelines, they have tended to vary from organization to

organization according to the perceived needs of the particular specialty.

The Society of Thoracic Surgeons has elected to develop guidelines that are brief, broadly interpretable, helpful to practicing clinical cardiothoracic surgeons, and useful to those assessing quality of cardiothoracic surgical care. After considerable deliberation and discussion, the guideline format developed by the American College of Obstetricians and Gynecologists[‡] was modified to fulfill the needs of practicing cardiothoracic surgeons and their patients. The guidelines were then developed and modified during an arduous review process. The general outline includes the following: Diagnosis, Procedure, Indication, Confirmation of Indication, Relative Contraindications, Actions Prior to Procedure, Actions During Procedure, Actions Following Procedure, Outcome and References. To make these guidelines relevant to cardiothoracic surgical practice, coding diagnoses with their codes and the procedure codes are indicated in each guideline. Lack of appropriate codes for newer procedures made coding difficult, if not impossible, in some instances.

From the inception of this task, it was acknowledged that practice guidelines could not and should not be all-inclusive. The development and application of guidelines must remain a dynamic process. Principles considered essential or important in a guideline at one time might become irrelevant or inappropriate at a later time. Extensively detailed and documented guidelines for the entire field of cardiothoracic surgery would approach the size of a textbook of cardiothoracic surgery, and would be obsolete before they were published.

Cardiothoracic surgical textbooks are updated frequently. Many of the Committee members have been contributors to these texts. Their selection as textbook contributors and Committee members acknowledges their clinical expertise in the field of cardiothoracic surgery. These guidelines have been developed by subcommittees of selected experts and educators, knowledgeable in the field of cardiothoracic surgery and especially the specific area to which they were assigned. Their curricula vitae will be available for review at the business office of The Society of Thoracic Surgeons.

As an initial entry into the field of practice guideline development, subcommittees in each of nine areas of the field of cardiothoracic surgery were charged with developing guidelines for three of the more commonly performed procedures in their designated area. These areas are: ischemic heart disease; valvular heart disease; thoracic aortic disease; transplantation and assist devices; arrythmias; bronchopulmonary disease; chest wall, diaphragmatic, mediastinal, and pericardial disorders; congenital heart disease, and esophageal disease.

After thorough deliberation, it was decided to have these guidelines procedure oriented. The thrust for development of these guidelines was to assure the opportunity for the best and most complete cardiothoracic surgical care for each patient. Issues of appropriateness and quality must be defined before cost can be assessed. The Committee is aware of its responsibility to each patient and to society to deliver this care in the most cost-efficient manner.

General recommendations that are applicable to the delivery of care to all cardiothoracic patients are presented separately. Basic preoperative evaluation and the necessary supporting services are identified in the following sections.

The Preoperative Evaluation

To be certain that the contemplated operation will not propose an undue risk to the patients, those who are candidates for a major thoracic or cardiac procedure should undergo a thorough preoperative evaluation. This evaluation is designed to detect concomitant medical diseases that might prove to contraindicate operation or that may require further treatment in preparation for the proposed surgical procedure. The following represents the minimum required preoperative evaluation and should be performed within one week of the date of operation.

1. Thorough history and physical examination
2. Chest roentgenogram
3. Urinalysis
4. Electrocardiogram
5. Blood sample for typing in all patients and a type and crossmatch for blood products in cases having a risk of significant blood loss. Patients who have previously provided blood via autologous donation may be excused from this requirement.
6. Blood analysis to include complete blood count, platelet count, PT, PTT and SMA-18.
7. Room air blood gas determination including pCO_2, pO_2, and pH in patients with suspected pulmonary compromise.
8. Appropriate medical consultation where indicated.
9. Assessment of nutritional status.

Institutional Requirements

There are certain institutional requirements that must be met if cardiothoracic surgery is to be safely performed within a health care center. These include:

1. Blood Bank—The performance of cardiac surgery necessitates an active and competently managed blood bank. At times, a blood bank may be called upon to provide large quantities of many different types of blood components with little or no notice. The presence of such a facility within the hospital is mandatory if major cardiothoracic surgery is to be performed safely.
2. Intensive Care Units—Adequate postoperative care often mandates complex equipment for treatment and the monitoring of many hemodynamic indices and

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[‡] Quality Assurance in Obstetrics and Gynecology; 1988 Edition, The American College of Obstetricians and Gynecologists, 409 12th St SW, Washington, DC 20024-2188.

other clinical parameters simultaneously. A hospital should have both the equipment for and medical, nursing, and ancillary personnel experienced in postsurgical critical care delivery if patient needs are to be met satisfactorily. Due to the needs for emergency intervention which occasionally arise in the postoperative period, there should be a physician on call within the hospital, preferably one with experience in the care of critically ill patients.

3. Anesthesiology—The safe performance of cardiothoracic surgical procedures requires a cooperative effort between surgeon and anesthesiologist. The critical nature of these patients and the multiple cardiopulmonary manipulations that inevitably occur require anesthesiologists who are expert in the delivery of care to patients with complex cardiac and thoracic problems. These anesthesiologists must be familiar with all types of ventilators, monitoring equipment, and other supportive equipment. Anesthesiologists with special interest in cardiothoracic surgical problems are preferable.
4. Operating Rooms—Both postoperative complications and primary cardiothoracic emergencies frequently require urgent operative intervention. An institution must therefore have the capability to rapidly mobilize surgical and support teams for emergency procedures 24 hours a day, seven days a week.
5. Medical Consultation Services—Supportive expertise must be available 24 hours a day, seven days a week in medical subspecialty fields such as cardiology, pulmonology, neurology, hematology, nephrology, and infectious disease.
6. Respiratory Therapy—The modern delivery of critical care requires around the clock availability of respiratory care personnel familiar with the operation, function, and maintenance of a wide variety of modern life support equipment.
7. Radiology—Around the clock radiologic services must be available in the fields of diagnostic radiology and nuclear medicine.
8. Laboratory and Pathology Services—Around the clock laboratory services must be available for immediate blood gas analysis and determination of serum biochemical and hematologic including coagulation values.

EDITOR'S NOTE:

This is the third set of guidelines to be published. The first set, on three procedures in the areas of chest wall, diaphragm, mediastinum, and pericardium, appeared in the April issue of *The Annals of Thoracic Surgery* (Ann Thorac Surg 1992;53:729–37). The second set, on three procedures for ischemic heart disease, appeared in the May issue (Ann Thorac Surg 1992;53:930–9).

Practice Guidelines

Esophageal Disease: I

Diagnosis:	530.6	Diverticulum of esophagus
Procedure:	43030	Cricopharyngeal myotomy
	43130	Diverticulectomy of hypopharynx or esophagus
	43135	Diverticulectomy—thoracic
	43136	Diverticulopexy of hypopharynx with or without myotomy
Indication:	1)	Dysphagia
	2)	Regurgitation with or without respiratory complications
Confirmation of Indication:	1)	Esophagogram
Relative Contraindications:	1)	No specific contraindications
Actions Prior to Procedure:	1)	Esophagogram
	2)	Esophagoscopy
	3)	Motility studies and/or pH monitoring for diverticula other than hypopharyngeal
Actions During Procedure:	1)	Appropriate myotomy
	2)	Maintain adequate esophageal lumen in area of repair
	3)	Test for air leak
Actions Following Procedure:	1)	Determine integrity of esophageal repair before discharge
Outcome:	1)	Mortality <1%
	2)	Improved swallowing
	3)	No further aspiration

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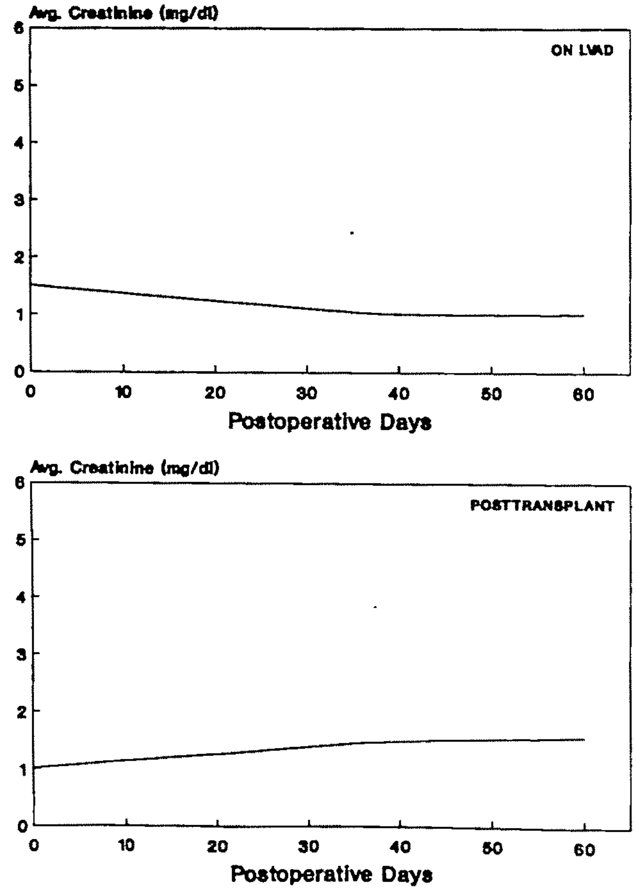

Fig 9. Average creatinine values were significantly greater at LVAD implantation compared with before transplantation. Creatinine levels were significantly greater on days 30 and 60 after transplantation than during ventricular support, presumably caused by immunosuppression.

of the 6 patients who died had been treated simultaneously with a Biomedicus (Biomedicus Inc, Eden Prairie, MN) right ventricular assist device. A statistical comparison of the patients who did versus those who did not bleed revealed no significant difference in outcome between the two groups with respect to transplantation and survival rates (Fisher's exact probability test; $p < 0.05$).

HEMOLYSIS. The average plasma free hemoglobin values for all the patients was 8.7 mg/dL. The hemoglobin concentration was 11.0 g/dL. Only 1 patient, a 50-year-old man who had a plasma free hemoglobin value of 40 mg/dL just before LVAD implantation, experienced hemolysis. His plasma free hemoglobin level exceeded 40 mg/dL on two consecutive occasions after implantation. He remained on the device for 66 days, underwent successful transplantation, and is currently alive and well several months after cardiac transplantation. Why hemolysis occurred before and after LVAD implantation is uncertain.

INFECTION. Infection was defined through detection of a positive culture, elevated white blood cell count, and fever, combined with the need for antimicrobial treatment. An infection was considered device-related if the specific organism that was cultured had not been detected preoperatively. Typical device-related infections involve the drive line or positive cultures isolated from the blood pump, coupled with the symptoms already described.

Based on the specified criteria, 7 (25%) of the 28 patients bridged to transplantation experienced a device-related infection. Six (85%) of the patients underwent transplantation, 4 (67%) of whom were long-term survivors. No significant difference existed between the outcome of infected and noninfected patients according to a Fisher's exact probability test ($p > 0.05$), suggesting that infection may not be a critical determinant of outcome.

Two of the 6 control patients (33%) experienced infections while awaiting transplantation. Although these patients did not receive an LVAD, the potential for infection was increased because of diagnostic instruments. The number of control patients was low, but the incidence of infection was high. It remains to be determined whether the presence of an LVAD further increases the risk of infection.

END-ORGAN DYSFUNCTION. As stated, all but two of the patients bridged to transplantation experienced renal or hepatic dysfunction or both before or during LVAD support. The dysfunction was not considered device-related in any of the patients.

RIGHT HEART FAILURE. Six (21%) of the 28 patients bridged to transplantation either required right ventricular assistance or exhibited symptoms of serious right ventricular dysfunction after implantation of the LVAD. Two of the patients experienced unanticipated right ventricular failure at the time of LVAD implantation but did not receive a right ventricular assist device. Although the LVAD is capable of generating flow rates of 6.0 L/min with 0.0 mm Hg inlet pressure, a low-flow condition persisted in both of the patients because of poor filling, and they died in the operating room. The inability to generate adequate flow under these circumstances was thought to be caused by an elevated pulmonary vascular resistance. The remaining 4 patients required right ventricular assistance, which was accomplished with the extracorporeal Biomedicus centrifugal pump. Two of the patients were electively weaned from the Biomedicus pump after 5 and 6 days, and 1 of these patients received a transplant. The other 2 patients requiring right ventricular assistance experienced progressively increasing pulmonary vascular resistance secondary to bleeding. All patients requiring right heart assistance ultimately died.

Among the adverse effects, right heart failure was the only complication that had a significantly negative correlation with outcome. When the patients with versus without right heart failure were compared, the transplantation rate and the survival rate were significantly lower for the patients who experienced right heart failure ($p < 0.05$).

THROMBOEMBOLISM. No device-related thromboemboli were observed in any of the patients. One patient, however, did experience an embolic event related to a mechanical aortic valve located in the natural heart. The patient recovered, underwent successful transplantation after 173 days of LVAD support, and was discharged home.

BOWEL ADHESIONS. Bowel adhesions to the Dacron-covered drive line occurred in 2 patients in whom the lead was allowed to course intraabdominally. Both patients underwent transplantation, but these two incidences emphasize the need to minimize contact between the bowel and the textured materials, such as Dacron.

MECHANICAL FAILURE. In 1988, a threaded outflow connector loosened after LVAD implantation in 1 patient, who required reoperation to tighten the connector. The design of the device was modified to incorporate a locking mechanism, and no additional adverse effects have been observed since that incident. This was the only failure in 7 patient-years of experience.

OVERALL. In summary, the frequency of device-related adverse effects has been low. Although a variety of patient-related adverse effects were observed, none aside from right heart failure had a negative correlation with outcome.

Quality of Life

The New York Heart Association classification system was used as a measure of quality of life in response to device support. All the LVAD-treated patients were in functional class IV at the time of implantation. Sixteen of the LVAD patients were alive at 60 days after transplantation, at which time 15 were in class I and 1 was in class II.

At the time of meeting study entrance criteria, 5 of the 6 control patients were in class IV, and the sixth patient was in class III. Only 1 of the control patients survived to 60 days after transplantation and was determined to be in class IV at that time. These data demonstrate that the quality of life of the LVAD-treated patients, based on functional class, was significantly improved during ventricular assistance and after transplantation. Also, the functional class of the LVAD-treated patients was markedly improved when compared with that of the control patients.

Comment

In contrast to extracorporeal LVADs that have been largely employed to support patients in acute cardiogenic shock or postinfarction, the HeartMate device has been used primarily for the extended support of patients with chronic cardiomyopathy who require a bridge to transplantation. Efficacy has been demonstrated by our study, in which the device provided adequate hemodynamic support until transplantation, increased survival, and improved the New York Heart Association functional class status of the patients. In comparison with the unsupported controls, the LVAD-treated patients had a better outcome. The majority of the LVAD-treated patients received transplants (65%), and 80% were discharged from the hospital after transplantation.

The ongoing clinical study will determine if the HeartMate LVAD performs in a safe and reliable fashion. Adverse effects, including bleeding, hemolysis, infection, peripheral end-organ dysfunction, and thromboembolic events, have not had a negative correlation with the rate of transplantation or survival. In contrast, acute perioperative right heart failure was associated with a significantly greater mortality.

In comparing complication rates with the HeartMate device with those reported in the Combined Registry [14], two important observations were noted. First, the average duration of support for the HeartMate patients was almost twice as long as that for the patients included in the Combined Registry report: 53 days versus 27.7 days. Second, the HeartMate patient population was composed primarily of end-stage cardiomyopathy patients, whereas those included in the Registry report were a combination of postcardiotomy, postinfarction, and cardiomyopathy patients. In general, the patients included in the Combined Registry report were experiencing acute left ventricular failure, whereas the HeartMate population was composed primarily of patients experiencing chronic left ventricular failure.

The nature and frequency of complications with the HeartMate were comparable with those reported for other devices, although the incidence of thromboembolic episodes was lower with the HeartMate. Previous reports estimate patient-related bleeding to occur in approximately 40% of LVAD-supported patients [13, 15], compared with a 39% rate of patient-related bleeding after implantation of the HeartMate. Infectious complications were more difficult to compare because no uniformity for reporting these data exists. Reported rates of infection range from approximately 20% to 75%, although not all of the infections were device-related [13, 15, 16]. In patients treated with the HeartMate, the incidence of device-related infection was 25%, yet 85% of the patients underwent transplantation, and their survival rate was 67%. It is noteworthy that a recent review of the literature from 12 transplant centers, encompassing 384 transplant patients treated with cyclosporine, showed that 57.6% of the patients experienced infections, with 5.2% dying of infection-related causes [17]. Two (33%) of the 6 control patients in the current study also had infections. These data appear to indicate that although the rate of infectious complications in both the LVAD-treated patients and the transplant patients is high, the number of infection-related deaths associated with both forms of treatment was relatively low. Whereas mediastinal infection was the primary cause of death in 40% of patients receiving a total artificial heart as a bridge to transplantation [18, 19], the risk of infection-related death with ventricular assistance appears significantly lower.

Thromboembolic complications have been a topic of great concern in the past decade, particularly in regard to the Jarvik-7 total artificial heart [20, 21]. Numerous reports of thromboembolic complications have also appeared in the ventricular assist device literature, with the rate ranging from 33% to 47% [15, 16, 22, 23]. No device-related thromboembolic events were observed in the HeartMate patients despite the use of minimal anticoagulative therapy. The only incident that occurred was related to a mechanical aortic valve in the native heart. The presence of a mechanical aortic valve may be considered a contraindication for use of an LVAD. The absence of thromboembolic complications with the HeartMate represents a major step forward for circulatory support systems toward minimizing the risk of device-related strokes.

Although it has been stated that left ventricular assistance may be potentially detrimental to right heart function [24, 25], additional reports have shown that impaired right ventricular function improves during left ventricular assistance [26]. Right ventricular function was indeed found to improve with left ventricular support in the majority of patients in this study, as evidenced by increased right ventricular ejection fractions. However, approximately 20% of the patients experienced severe right ventricular dysfunction at implantation, which increased mortality and morbidity in comparison with patients who had no right ventricular involvement. The inability to fill the pump in the presence of right ventricular failure has been attributed to concomitant elevated pulmonary vascular resistance. Use of prostaglandins [27] combined with other pharmacologic measures may aid in reducing pulmonary vascular resistance, but additional study is required. Currently, right ventricular dysfunction appears to be a significant contraindication for left ventricular support.

The onset of renal failure shortly before or during ventricular assistance has been suggested to be highly predictive of a poor prognosis [28]. However, both the Thermo Cardiosystems Inc and Novacor devices have successfully supported patients who were anuric before implantation and on hemodialysis for prolonged periods (months) followed by successful transplantation and survival [13]. Renal failure has been regarded as a contraindication for patients in acute left ventricular failure, but it is not clear that it should be considered a contraindication for chronic cardiomyopathy patients.

Hepatic function was shown to improve significantly with hemodynamic support, but up to 2 months of LVAD support was required for hepatic function to return to normal. The patients had better hepatic and renal function just before transplantation than before LVAD implantation. This improvement was a result of using the device. Beyond implantation, no difference in hepatic function was observed when the two treatments were compared. In contrast, creatinine values were shown to be significantly higher in the transplant patients after 30 to 60 days of the operation than in the LVAD patients at comparable times after initiation of ventricular assistance. The rise in creatinine level was attributed to the use of immunosuppressive drugs after transplantation.

In conclusion, the HeartMate 1000 IP LVAD has been shown to provide an effective means of supporting patients for periods in excess of 300 days. The study will continue to be expanded to include additional patients and controls to further assess safety and effectiveness of this technology as a bridge to transplantation.

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Notice From the Southern Thoracic Surgical Association

The Thirty-ninth Annual Meeting of the Southern Thoracic Surgical Association will be held at the Saddlebrook Golf and Tennis Resort, Wesley Chapel (near Tampa), Florida, November 5–7, 1992. The Postgraduate Course will be held the morning of Thursday, November 5, 1992, and will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Applications for membership should be completed by August 1, 1992, and forwarded to John P. Clarke, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267.

Hendrick B. Barner, MD
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Efficacy of a Hydroxyl Radical Scavenger (VF 233) in Preventing Reperfusion Injury in the Isolated Rabbit Heart

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We tested the hypothesis that 3,4,5,-trihydroxybenzamidoxime (VF 233), a demonstrated hydroxyl radical scavenger and an effective Fe^{3+} chelator, attenuates reperfusion injury and improves isovolumic left ventricular function. Eighteen isolated, perfused rabbit hearts with intracavitary balloons were subjected to normothermic, global ischemia until the initiation of ischemic contracture. Effects on the adenine nucleotide pool metabolites were determined by high-pressure liquid chromatography from right ventricular biopsy specimens before ischemia and at 15-minute intervals throughout reperfusion. In the experimental group (n = 9), a 5-mL bolus of 1 mol/L VF 233 was given immediately before reperfusion and followed by a continuous infusion (0.125 μmol/min). The control group (n = 9) received the vehicle solution at identical times. Rabbits treated with VF 233 had significant improvement in left ventricular function (expressed as percent return of left ventricular peak developed pressure) within 15 minutes of reperfusion (55.0 ± 3.0 versus 66.2 ± 4.1; $p < 0.05$ by analysis of variance) after global ischemia and remained significantly improved throughout the reperfusion period. Myocardial adenine nucleotide pool intermediates were not significantly different between groups. These results demonstrate that administration of VF 233 significantly improves ventricular function but does not affect adenine nucleotide metabolism after ischemia and reperfusion.

(Ann Thorac Surg 1992;53:1091–5)

Myocardial contractile dysfunction associated with reperfusion has been attributed to many interrelated factors. Free radical species are thought to be a major cause of reperfusion injury. Reoxygenation initiates the formation of active oxygen species such as the superoxide radical ($\cdot O^-_2$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH\cdot$). The hydroxyl radical is usually considered one of the most cytotoxic species of free radicals because of its strong oxidizing properties. Unlike the superoxide radical, no physiologic scavenging mechanism has been identified for the hydroxyl radical [1–6]. The primary mechanism of clearance of $\cdot O^-_2$ from biologic systems is superoxide dismutase, which catalyzes the dismutation of $\cdot O^-_2$ to H_2O_2 and H_2O [2]. Several studies have demonstrated that functional recovery of the ischemic myocardium is enhanced by agents that either scavenge oxygen free radicals, such as superoxide dismutase and catalase [3–5], or chelate iron, such as deferoxamine and dimethylthiourea [6]. Prevention of hydroxyl radical–mediated injury may therefore be hypothesized to improve postischemic ventricular function. The optimum pharmacologic strategy to minimize oxygen-derived free radical–mediated reperfusion injury is not clear.

3,4,5,-Trihydroxybenzamidoxime (VF 233), one of the polyhydroxyphenyl derivatives, originally was developed as an antitumor agent due to its ribonucleotide reductase inhibiting activity and free radical scavenging ability [7–11]. This study tested the hypothesis that the polyhydroxylphenyl derivative VF 233 attenuates hydroxyl radical–mediated reperfusion injury and thereby improves postischemic ventricular performance. Experiments were performed using the isolated, perfused rabbit heart model to evaluate the effect of VF 233 on postischemic left ventricular function.

Materials and Methods

Eighteen healthy New Zealand White rabbits weighing 3.5 to 4.0 kg were studied. Rabbits were sedated with xylazine (20 mg/kg) and anesthetized with ketamine (50 mg/kg). Tracheostomy was performed, and the animals were mechanically ventilated throughout cardiectomy. After median sternotomy, the rabbits received heparin through the right atrial appendage. Hearts were rapidly excised and mounted on a modified Langendorff isolated heart preparation [12]. Time from cardiectomy to perfusion on the isolated heart apparatus was less than 30 seconds for all experiments. Hearts were perfused in a nonrecirculating manner with a modified Krebs-Henseleit buffer solution at a pressure of 100 cm H_2O and a pH of 7.4 ± 0.02 which was equilibrated with 95% oxygen and 5% carbon dioxide and contained (in millimoles per liter):

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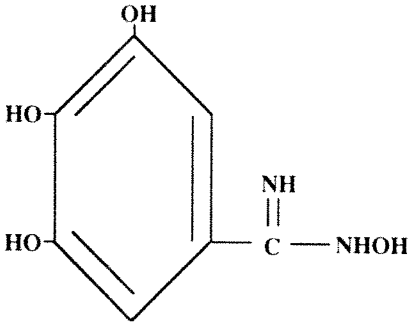

Fig 1. The chemical structure of 3,4,5,-trihydroxybenzamidoxime (VF 233).

NaCl, 13.85; $NaHCO_3$, 4.2; KCl, 0.71; KH_2PO_4, 0.32; $MgSO_4$, 0.59; $CaCl_2$, 0.55; and dextrose, 3.96 [13]. Left ventricular pressure was measured with a water-filled latex balloon inserted into the left ventricle through the mitral valve. Hearts were maintained at 37°C throughout the study. Hearts were atrially paced at 180 beats/min using suprathreshold rectangular pulses of 1.0 ms duration.

After a 15-minute stabilization period, a Frank-Starling curve was created by sequentially increasing the intraventricular balloon volume. The balloon volume that resulted in the greatest developed pressure was identified and maintained throughout the study. After baseline hemodynamic data were gathered, hearts were subjected to a period of global, normothermic ischemia until the initiation of ischemic contracture, defined as a 4 mm Hg rise in intraventricular pressure after cardiac arrest. Left ventricular functional recovery after ischemia was quantified by measuring the percent return of developed pressure compared with baseline. Postischemic left ventricular function, expressed as percent return of left ventricular developed pressure, was recorded at 15-minute intervals throughout reperfusion. After stabilization of the isolated heart preparation, a 5-mL bolus of 1 mmol/L VF 233 (Fig 1) (generously supplied by Molecules for Health, Inc, Richmond, VA) was administrated immediately before reperfusion and followed by a constant infusion (0.125 μmol/min) in the experimental group ($n = 9$). The control group ($n = 9$) received the vehicle solution at identical times.

Myocardial adenine nucleotide content along with adenosine triphosphate (ATP) catabolites were measured from right ventricular biopsy specimens obtained at baseline before ischemia, immediately before reperfusion, and after 30 and 60 minutes of reperfusion. Biopsy specimens were immediately frozen in liquid nitrogen for storage. Determination of myocardial adenine nucleotide content along with protein content were performed as described previously [14]. Briefly, each biopsy specimen was extracted in 12% trichloroacetic acid (4°C) for 30 minutes with frequent homogenization. The soluble acid extract was separated from denatured protein by centrifugation and neutralized with a tri-*n*-octylamine-freon mixture. Protein content of the pellet was determined as previously described [15]. The neutralized extracts were stored at −70°C. Myocardial adenine nucleotide pool intermediates were determined using high-pressure liquid chromatography and expressed as nanomoles per milligram protein.

All statistical analysis was performed with personal computer–based software from the SAS Institute (Cary, NC). Results are expressed as mean ± standard error of the mean. Comparison of data obtained at multiple time points to baseline was performed using analysis of variance for repeated measures. Student's *t* test for unpaired data was used where appropriate.

Results

Before ischemia at 37°C, developed pressure was 113.3 ± 3.9 mm Hg in control hearts and 101.7 ± 5.25 mm Hg in VF 233–treated hearts (p = not significant). The mean interval that elapsed before the onset of ischemic contracture in the control group was not significantly different from the time to ischemic contracture in the experimental (VF 233) group (17.50 ± 1.23 versus 16.13 ± 1.52 minutes). After normothermic ischemia, all hearts resumed beating spontaneously in a regular rhythm and did not require defibrillation.

Peak developed pressure and end-diastolic pressure were recorded before ischemia (baseline) and after 15, 30, 45, and 60 minutes of reperfusion. Percentage of peak developed pressure was calculated for each period of reperfusion as the ratio of peak developed pressure to baseline preischemic peak developed pressure (Figs 2, 3).

At 15 minutes of reperfusion, control hearts recovered 55.00% ± 3.04% of baseline developed pressure before gradually rising to 66.3% ± 2.18% at 60 minutes of reperfusion. In contrast, VF 233–treated hearts recovered 66.2% ± 2.18% of baseline developed pressure within 15 minutes of reflow and 82.3% ± 3.57% by the end of the 60-minute reperfusion period ($p < 0.01$ by analysis of variance) (see Fig 2). End-diastolic pressure at time 0 was similar in both groups (4.7 ± 0.8 versus 5.2 ± 1.2 mm Hg). After 15 minutes of reperfusion, differences between groups were not statistically significant (see Fig 3).

Myocardial adenine nucleotide levels before and after VF 233 or vehicle administration, at the end of ischemia, and during reperfusion are shown in Table 1. The mean preischemic levels of myocardial ATP in the VF 233 and control groups were similar. There were no significant differences in myocardial adenine nucleotide pools between the two groups. Levels of ATP metabolites over time are presented in Table 1.

Comment

The harmful action of oxygen-derived free radicals after ischemia and reperfusion has been well described [1–6, 16]. The hydroxyl radical is capable of causing extensive oxidative cellular damage. Hydroxyl radical generation results from a reaction between the one-electron reduced superoxide anion and the two-electron reduced hydrogen peroxide. This reaction is the Haber-Weiss reaction and requires the participation of a transition metal catalyst, usually iron [17]. Several agents such as mannitol, di-

Practice Guidelines

Esophageal Disease: II

Diagnosis:	150	(150.0–150.9) Malignant neoplasm of esophagus
Procedure:	43110	Esophagectomy—gastric anastomoses
	43115	Esophagectomy—segment replacement, one or two stages
	43119	Total esophagectomy without thoracotomy
	43120	Esophagogastrectomy
Indication:	1)	Histologically proven malignancy of esophagus
Confirmation of Indication:	1)	Endoscopic visualization of tumor
Relative Contraindications:	1)	Distant metastatic disease
	2)	Histologic confirmation of tracheal or bronchial involvement
Actions Prior to Procedure:	1)	Esophagogram
	2)	Esophagoscopy
	3)	Bronchoscopy for upper or middle third tumors
	4)	Discuss treatment options with patient and family
	5)	CT scan of chest and upper abdomen
Actions During Procedure:	1)	Determine resectability
	2)	Removal of primary tumor and documentation of margins by frozen section
	3)	Restoration of GI continuity when possible
Actions Following Procedure:	1)	Determine integrity of anastomosis before discharge
Outcome:	1)	Mortality <10%
	2)	Serious complication rate <30%
	3)	Resumption of oral intake

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Practice Guidelines

Esophageal Disease: III

Diagnosis:	150	(150.0–150.9) Malignant neoplasm of esophagus
Procedure:	43200	Esophagoscopy, rigid or flexible
	43202	Esophagoscopy for biopsy, brushing, or washing
	43217	Esophagoscopy for removal of polypoid lesion
	43219	Esophagoscopy for insertion of plastic tube or stent
	43220	Esophagoscopy for dilation
	43226	Esophagoscopy for insertion of guidewire
	43228	Esophagoscopy for ablation of tumor (electrocoagulation or laser photocoagulation)
Indication:	1)	Abnormal esophagogram or symptoms of obstruction or bleeding
Confirmation of Indication:	1)	Abnormal esophagogram
Relative Contraindications:	1)	No specific contraindications
Actions Prior to Procedure:	1)	Esophagogram
Actions During Procedure:	1)	Establish diagnosis
	2)	Evaluate resectability
	3)	Evaluate response to chemotherapy, radiation therapy, or surgery
	4)	Palliate obstructive tumor
Actions Following Procedure:	1)	Observe for chest pain, subcutaneous emphysema, or fever
	2)	Chest roentgenogram and/or contrast study of esophagus if indicated
	3)	Observe for respiratory difficulty
	4)	Observe for bleeding
Outcome:	1)	Mortality—according to procedure

43200/43202	<0.1%
4321	<1.0%
43219	<25%
43220	<5%
43226	<1%
43228	<25%

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CORRESPONDENCE

Cystic and Bullous Lung Disease

To the Editor:

The current review written on the subject of cystic and bullous disease by R. R. Klingman and associates [1] is excellent, as it insists on the difficulties in determining indication for operation, especially in those patients whose whole lung is more or less deteriorated, which is the case in more than 90% of our patients in northern France. Klingman and associates state that isolated bullae in asymptomatic patients should be observed. This has been our dilemma considering what we call "giant bullae," ie, filling at least one third of a hemithorax.

For a first group of 58 patients admitted to our surgical unit, 23 cases of bulla(e) had first been discovered on a chest roentgenogram before the appearance of any symptom, but in this subgroup only 4 patients of 23 were symptomless when operated on. The delay between the clinical or radiological discovery of the bulla(e) and operation varied between 0 and 12 years (mean, 3 years 3 months). Finally, at the time of operation, 41 patients were suffering from an increasing dyspnea, and in 22 of them the bulla(e) had increased in size. One or several episodes of pneumothorax (32 in 1 patient!) had been treated in 13 patients. Recurrent lung infection had happened in 10 patients. Infection of a bulla had occurred in 3 patients, and an abnormal opacity had appeared in a bulla or by a bulla in 5 patients (1 cancer). In 12 patients of 58, one bulla occupied at least two thirds and in 9 patients at least one half of a hemithorax. In 18 patients, bullae were bilateral. Five patients had a cor pulmonale.

Of the 18 patients with bilateral bullae, 7 had operation on both sides, and 11 had operation on one side. Among the latter 11 patients, 3 died of contralateral complications, 2 had a secondary contralateral bullectomy, 1 developed tuberculosis and was not reoperated on, and 5 still have a contralateral bulla (filling less than half the hemithorax) which has remained identical after 1, 2, 3, and 5 years.

In a second group of 17 patients admitted to the intensive care pneumology unit because of acute respiratory distress, all were mechanically ventilated: 6 had a tube in the pleura, 2 in the bulla, and these 8 patients had an important air leak. The reasons for the sudden deterioration were a pneumothorax in 6, an important volume increase of the bulla in 4, an infection in 4, a bronchospastic dyspnea in 2, and a hemorrhage within a bulla with hemoptysis in 1. In 11 patients bullae were bilateral. Seven patients had a cor pulmonale. However, only 11 of these 17 patients had had an alarming former respiratory clinical story: 6 had bullae that had been radiological discoveries, with no symptoms or with discrete symptoms before the acute complication happened. The delay between the discovery of the bulla(e) and the complication was between 0 and 14 years (mean, 4 years 9 months). Eight of those 17 patients died, all with bilateral bullae operated on one side in 5 cases, on both sides in 3 cases, six with a cor pulmonale!

These results show that giant bullae may be symptomless, but remain so in a minority of cases, and that symptomless bullae can suddenly become complicated and cause death in spite of emergency operation. What is the surgical indication for preventive operation in symptomless unilateral or bilateral bullae?

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Reference

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Reply

To the Editor:

My colleagues and I would like to thank Dr Ribet for his comments. Unfortunately, at the time of this current review, Dr Ribet's data were not yet available and may clarify the selection for operation in patients with large asymptomatic bullae.

However, numerous studies have been published regarding the results of surgical management of symptomatic bullous lung disease. All series demonstrate a substantial mortality and morbidity including empyema, incomplete reexpansion, and prolonged or persistent air leaks.

Although clear guidelines remain to be defined for the selection of patients with large asymptomatic bullae for "preventive" operation, the high incidence of postoperative complications leads us to conclude symptomless unilateral and bilateral bullae should be observed.

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Histology of the Internal Mammary Artery Versus the Inferior Epigastric Artery

To the Editor:

In response to the excellent recent study of Barner and coworkers [1], in which both the internal mammary artery (IMA) and the inferior epigastric artery (IEA) were histologically examined, we would like to add some modifications to their description of the histological pattern of the IMA. Although our group initially had classified the IMA as an elastic artery, we subsequently have reported a varying histological pattern of the IMA along its course from the subclavian artery to the epigastric bifurcation: in the majority of the patients in our study the media of both the proximal and distal segments was elastomuscular and that of the mid segment primarily elastic (Fig 1), whereas that of the musculophrenic artery and the superior epigastric artery, in which the IMA continues, was almost purely muscular [2, 3]. Barner and colleagues did not mention whether the histological specimens of the IEA that they studied were from the proximal, mid, or distal part of the artery, nor did they specify how far distal to the epigastric bifurcation (if at all) the IMAs were harvested. Usually, the media of the proximal IEA is muscular, with rare elastic lamellae in the first few centimeters from its origin at the external iliac artery. Thus, Barner and associates' suggestion that the IMA and IEA are histologically similar may simply reflect the fact that distal IMA specimens were compared with proximal IEA specimens. In addition, the deviation of the usual (distal) elastomuscular pattern of the IMA to an almost purely muscular pattern and of the usual muscular pattern of the IEA (Fig 2) to an elastomuscular pattern in 2 and 3 of their patients, respectively, may also reflect different harvesting sites of the specimens or interindividual variability in histological pattern in both arteries.

The internal elastic lamina of the IEA, with regard to the

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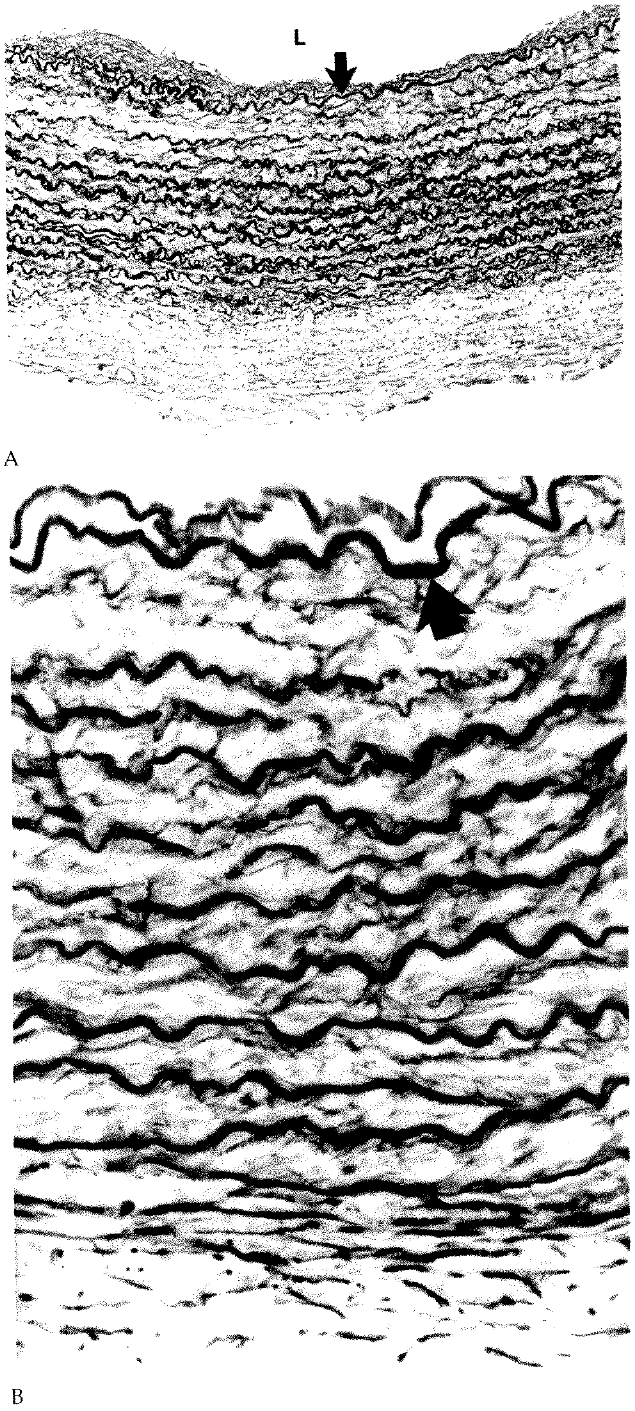

Fig 1. (A) Example of midsegment of internal mammary artery. (B) Detail. Note the multiple elastic lamellae in the media. (Elastin-trichrome after Masson stain; (A) ×140 before 31% reduction; (B) ×400 before 3% reduction.) (Arrow = *internal elastic lamina;* L = *lumen.)*

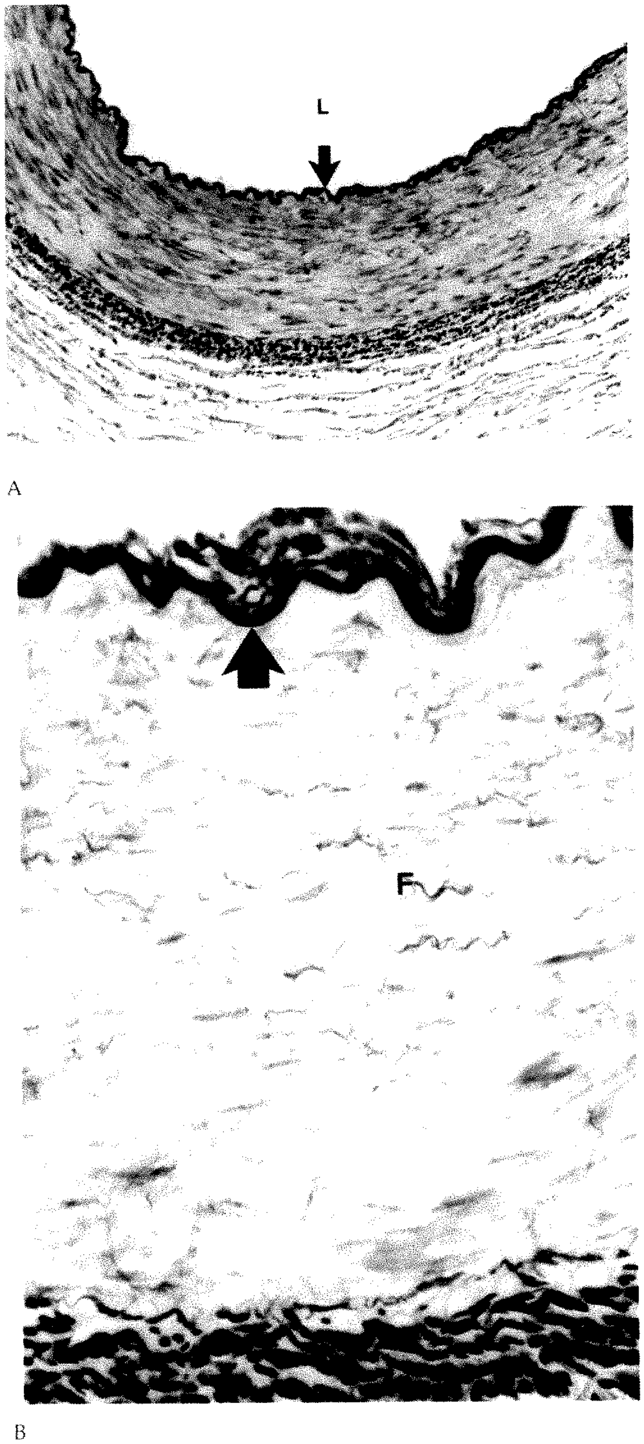

Fig 2. (A) Example of midsegment of inferior epigastric artery. Pronounced internal elastic lamina is evident (arrow). *(B) Detail. Note the primarily muscular media and the scant amount of elastic fibrils in it. (Elastin-trichrome after Masson stain; (A) ×140 before 32% reduction; (B) ×400 before 3% reduction.)* (F = *elastic fibril;* L = *lumen.)*

number of discontinuities in it, is generally similar to that of the (elasto)muscular segments of the IMA. In contrast, in the elastic segments of the IMA we generally observed less discontinuities in the internal elastic lamina (van Son JAM, Smedts F; unpublished results).

We hypothesize that the higher elastic content of the media of the IMA versus the IEA not only provides more protection from the formation of discontinuities of the internal elastic lamina, and hence from intimal thickening, but also considerably influences the degree of vasospasm. Therefore, we are not surprised that Barner and co-workers encountered a higher degree of spasm in the IEA than in the IMA during harvesting. Their report of a propensity toward spasm of the IEA is analogous to studies in which other muscular arterial conduits, such as the right gastroepiploic, the musculophrenic, and the superior epigastric artery, were examined [4–6].

We agree with Dr Mills, who discussed Dr Barner's paper at the Twenty-seventh Annual Meeting of The Society of Thoracic Surgeons, that in the majority of patients the IEA should probably not be used to bypass the left anterior descending coronary artery, because the latter artery is generally the most important vessel supplying the myocardium. Because of the anticipated enhanced propensity of the IEA toward intimal thickening, in comparison with the IMA, once exposed to the vigorous hemodynamics in the vicinity of the heart, the long-term results of myocardial revascularization with the IEA in terms of patency rate may probably be less superior than those obtained with the IMA. Indeed, as Barner and associates suggest, long-term patency curves must be established before widespread use of the IEA can be confidently advised.

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Patent Foramen Ovale: A Cause of Hypoxemia in Patients on Left Ventricular Support

To the Editor:

We read with great interest the article by Baldwin and associates [1] and would fully agree on the importance of a patent foramen ovale as a cause of hypoxemia in patients on left ventricular support. In fact, we recommended in an article published in 1986 [2], which detailed 3 case reports, that taking the extra time to identify and close a patent foramen ovale at the time of operation could avoid this potentially fatal complication. We were somewhat surprised to note that this experienced group omitted reference to this contribution in their review of the English-language literature from 1966 to the present.

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References

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Reply

To the Editor:

Magovern and associates' report on the patent foramen ovale during left ventricular assist pumping from 1986 does indeed antedate Dr Kyo's report from 1989. Credit for the first description of this potentially lethal complication should, therefore, go to Drs Magovern, Pae, Richenbacher, and Pierce instead of Dr Kyo's group as we had mistakenly stated in our manuscript.

In our Medline search, numerous terms for left ventricular assist devices were used but we did not search the phrase "left ventricular assist pumping," which would have led us to this important report. It was our focus to recommend the selective use of contrast-enhanced transesophageal echocardiography for the patient on left ventricular support with unexplained arterial hypoxemia.

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Radial Nerve Injury in Patients Undergoing Coronary Artery Bypass Grafting

To the Editor:

Three male patients aged 58, 64, and 67 years underwent myocardial revascularization that included mobilization of the left internal mammary artery using a single-stem sternal elevating retractor. In the early postoperative period, each complained of extensor weakness at the left wrist and, in 2 of the patients, nerve conduction studies confirmed a radial nerve lesion in the upper arm. Nerve conduction studies were not performed in the third patient. All three patients demonstrated substantial improvement at follow-up 6 weeks after operation and went on to make a full recovery.

The radial nerve originates as a terminal branch of the posterior cord of the brachial plexus behind the axillary artery and enters the posterior compartment of the arm between the long head of the triceps and the humeral shaft to run with the profunda brachii artery in the radial groove of the humerus.

Peripheral nerve injuries are relatively common during cardiac operations [1, 2], and radial nerve palsy after coronary artery

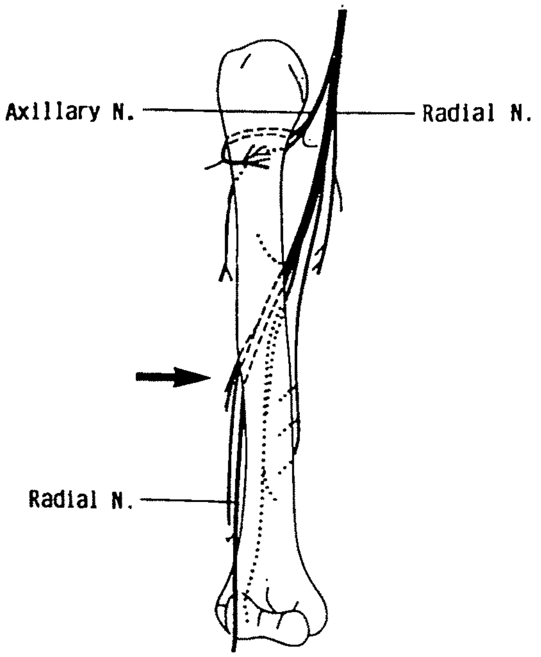

Fig 1. Diagram of radial nerve and its branches to show site of injury by retractor stem.

bypass grafting has previously been reported [2] although the cause was not specified. In each of our patients, the left internal mammary artery was mobilized from the thoracic wall using a retractor with a single central stem fixed to the operating table with a clamp, and a T-bar from which the two sternal elevating hooks were suspended. We believe that this stem can cause a neuropraxia by local pressure on the radial nerve (Fig 1), particularly as the vulnerable section of the nerve is at a level with the middle of the sternum and hence at the optimum position for the retractor stem.

Several types of sternal elevating retractor are available, and the single-stem type is said to have the advantage of easy relocation for mobilization of the contralateral mammary artery [3, 4]. We suggest that this nerve injury can be avoided by careful protection of the upper arm with pads when using a retractor of this type. Particular care is required with an obese patient to ensure that the arm does not overhang the side of the operating table.

Other methods of sternal retraction [5–8] are well described, and we have never experienced this complication in a larger group of patients in whom the mammary artery was mobilized using a retractor with two stems, one positioned at each end of the cross-bar, thus entirely avoiding the area of the radial nerve.

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Nonabsorbable Interrupted Sutures for Tracheal Anastomosis in Childhood

To the Editor:

In a recent issue of *The Annals*, McKeown and associates [1] presented an experimental study on tracheal anastomosis in rabbits and concluded that absorbable suture material combined with interrupted sutured technique proved to be significantly superior to other methods in avoiding postoperative narrowing.

I successfully used interrupted nonabsorbable suture several years ago in a 5-year-old boy admitted for severe tracheal obstruction after congenital aplasia of three cartilaginous rings. The narrowing, already evident on chest roentgenogram (Fig 1), was better defined by tomography. The patient underwent a 3.5-cm-long resection just above the carina, and the two tracheal stumps were approximated with 3-0 interrupted Vitalon (Deknatel, Neustadt, Germany) stitches; the procedure was completed by overriding the suture line with a pleural flap. A fibrin glue (Tissucol; Immuno AG, Vien, Austria) was then used to keep the tissues firm, preventing a possible air leak. Because of the extensive resection, cervical flexion after the anastomosis was maintained with large sutures between the skin of the chest and chin. Extubation was performed soon after the operation, and cervical flexion was ended after 7 days. The postoperative course was uneventful. Three years later the patient was free of symptoms. No sign of inflammatory reaction or dehiscence was seen at bronchoscopy, and tomography showed a widely patent anastomosis (Fig 2).

My experience suggests that nonabsorbable suture material can also be successfully employed in childhood, even when an extensive tracheal resection is required.

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Reference

1. McKeown PP, Tsuboi H, Togo T, Thomas R, Tuck R, Gordon D. Growth of tracheal anastomoses: advantage of absorbable interrupted sutures. Ann Thorac Surg 1991;51:636–41.

Reply

To the Editor:

I congratulate Dr Santoli for a successful outcome in tracheal reconstruction in a 5-year-old boy with congenital aplasia. The

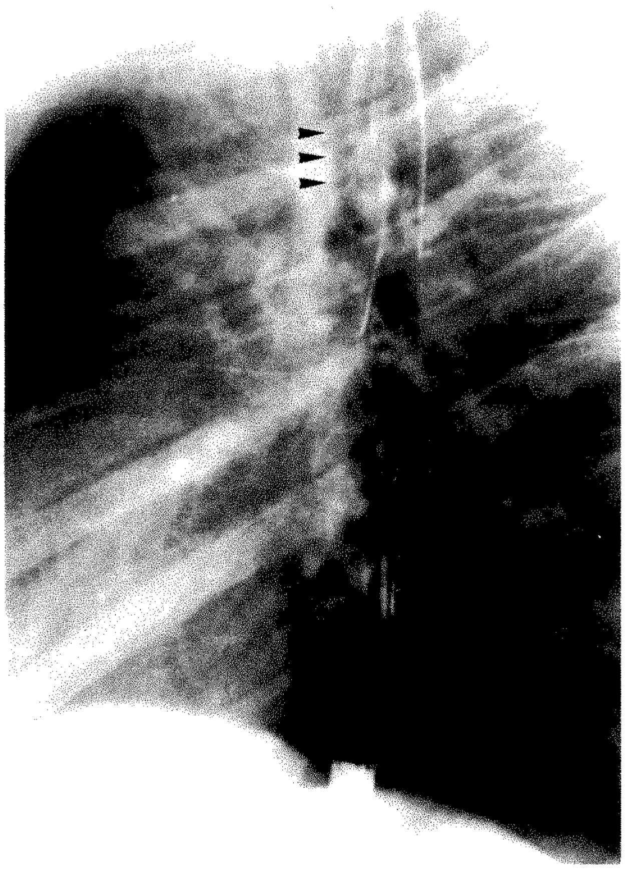

Fig 1. Lateral roentgenogram showing the distal tracheal narrowing.

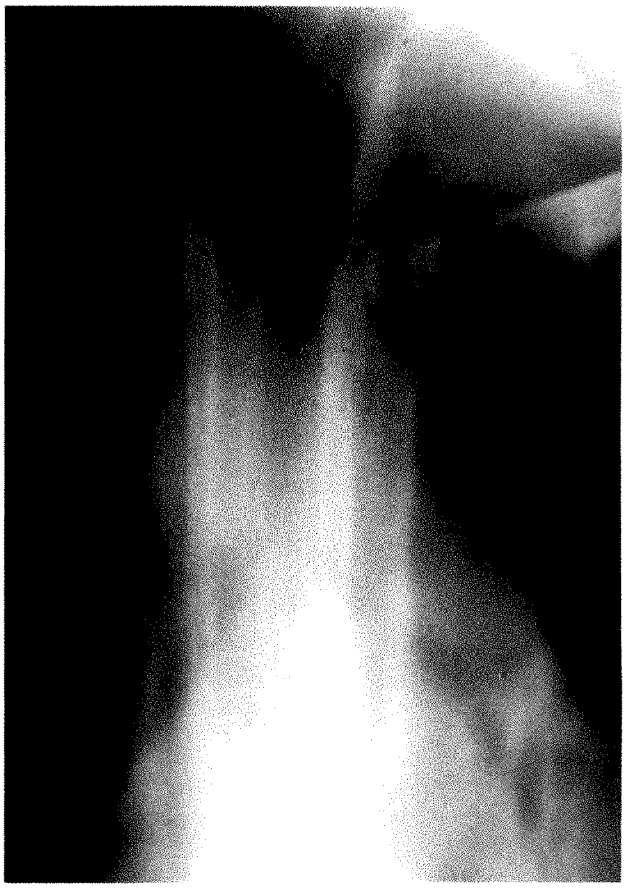

Fig 2. Three years after operation, the tracheal anastomosis is fully patent.

repair was performed with interrupted, nonabsorbable sutures. Doubtless there have been other successful repairs under similar conditions.

In our research study [1] our aim was to analyze what was the best method and best suture material under extreme conditions, and in this animal study interrupted PDS proved to be superior to continuous PDS or interrupted or continuous polypropylene. In this experimental study the body weight of the animals increased by 125%. Dr Santoli does not list increases in height and weight of his patient, but on the basis of data from the National Center for Health Statistics (NCHS, Hyattsville, MD) I would suspect that the child's increase in weight was approximately 30% and height probably 15% over the 3-year period. I think longer follow-up would be necessary to absolutely exclude compromise of the lumen of the trachea at the repair site.

Our intention with the research study was not to condemn the use of interrupted, nonabsorabable suture but to try to elucidate the most optimal method and suture for doing tracheal anastomoses in children. Although isolated clinically successful outcomes may be achieved using different methods and materials, we stand by the results of our study.

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Reference

1. McKeown PP, Tsuboi H, Togo T, Thomas R, Tuck R, Gordon D. Growth of tracheal anastomoses: advantage of absorbable interrupted sutures. Ann Thorac Surg 1991;51:636–41.

Open Coronary Endarterectomy, Saphenous Vein Patch Reconstruction, and Internal Mammary Artery Grafting

To the Editor:

We read with interest the recent article by Ladowski and coworkers [1] entitled "Endarterectomy, vein patch, and mammary bypass of the anterior descending artery." They described a technique that we employed for the first time in 1985 [2, 3]. Up to now in our department 48 patients with diffuse anterior descending coronary artery disease have undergone myocardial revascularization with open endarterectomy, coronary reconstruction with a tailored saphenous vein patch, and subsequent internal mammary artery to vein patch anastomosis.

A recent review of our whole experience with this technique [4, 5] including 38 procedures on the anterior descending coronary artery, 7 on the right coronary artery, and 1 on the circumflex artery did not confirm an increase of perioperative risk and an uncertain long-term benefit of coronary endarterectomy in comparison with standard coronary artery bypass grafting [6]. There was one perioperative death (2.1%) and one perioperative myocardial infarction. The mid-term and long-term clinical results were not much different than those obtained with conventional coronary bypass: the 5-year survival rate was 86.8% and the freedom from angina after a mean follow-up of 35 months was 75.6%. Several patients have been subjected to angiography in the postoperative period and during the follow-up. The early patency was 92.5% (25/27). A second angiographic control was performed between 30 and 36 months after the operation, reporting a patency rate of 81.5% (13/16). Further angiography performed between 54 and 60 months postoperatively in 5 of 9 patients did not show any additional occlusion.

Our experience supports the conclusions of Ladowski and co-workers. We consider this technique the only worthwhile method for providing myocardial revascularization in patients with diffuse coronary artery disease.

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Reply

To the Editor:

We were delighted to learn of the prior independent application and excellent outcome of the technique of endarterectomy, vein patch, and mammary bypass of the anterior descending artery as practiced by Doctors Lemma, Beretta, Vanelli, and Santoli. We believe that their results serve to encourage us further to apply this technique to the coronary artery that is otherwise nonreconstructible. We salute Doctor Lemma's excellent results.

The only statement that we take exception to is that this technique is "the only worthwhile method for providing myocardial revascularization in patients with diffuse coronary artery disease." Certain patients with diffuse coronary artery disease have benefited in our institution from other techniques (such as percutaneous transluminal atherectomy, bypass of the endarterectomized artery with saphenous vein when internal mammary artery conduits are unavailable, and reconstruction of the endarterectomized coronary artery with a long internal mammary artery to coronary bypass). Certainly, however, this technique is a *good* tool for reconstructing the diffusely diseased coronary artery. Fortunately, it remains one of *many* tools.

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Semb Ligature Carrier

To the Editor:

Sugarbaker and Mentzer [1] describe the use of the "Semm" clamp while stapling hilar vessels in the performance of pneumonectomy. The appellation "Semm" is incorrect.

The correct name for the instrument is the Semb ligature carrier. It was devised by Carl Semb of Oslo, a pioneer in the treatment of tuberculosis. Dr Semb is noted for his development of the technique of extrafascial apicolysis, as well as the surgical treatment of renal tuberculosis. Dr Semb was an Honorary Member of the American Association for Thoracic Surgery. I suspect that he devised the ligature carrier to encircle and control the renal hilum. As Sugarbaker and Mentzer note, the Semb clamp is indeed a valuable instrument in thoracic surgery.

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EDITOR'S NOTE

Dr Fell is indeed correct. Like Dr Fell, I trained and worked principally in the days before the stapling devices, and found the Semb ligature carrier to be one of the most useful instruments on the Mayo table. We should have detected this mistake, and *The Annals* apologizes for the error.

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Volume 53 (January–June 1992)

KEY TO ABBREVIATIONS USED FOR ARTICLE CLASSIFICATION

* = Original Article
AN = Announcement
CL = Classics in Thoracic Surgery
CR = Case Report
CP = Correspondence
CT = Collective Review
CV = Current Review
DI = Discussion
ED = Editorial
HW = How to Do It
IC = Invited Commentary
KR = Key References
PA = Presidential Address
RE = Report
RV = Review of Recent Books
TR = Tribute
UP = Update

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* = Original Article
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CL = Classics in Thoracic Surgery
CR = Case Report
CP = Correspondence
CT = Collective Review
CV = Current Review
ED = Editorial
HW = How to Do It
KR = Key References
PA = Presidential Address
RE = Report
RV = Review of Recent Books
TR = Tribute
UP = Update

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Sequential Silastic and expandable metal stenting for tracheobronchial strictures (Tsang, Williams, & Goldstraw) 1992; 53:856–60*

Bronchial fistula

Endobronchial closure of postpneumonectomy bronchopleural fistula (Opie, Vaughn, & others) 1992;53:686–8,CR

Esophagobronchial fistula associated with corrosive stricture of the esophagus (Rakić & Cerzić) 1992;53:142–3,CR

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Granulocyte sequestration and early failure in the autoperfused heart-lung preparation (Genco, Connolly, & others) 1992;53:217–26*

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Bronchoscopic appearance after single-lung transplantation (Eng, Sabanathan, & Newton) 1992;53:181–2,CP

Bupivacaine

Intrapleural bupivacaine in the control of postthoracotomy pain (Mann, Young, & others) 1992;53:449–54*

Burns, chemical

Esophageal reconstruction for esophageal strictures or resection after corrosive injury (Wu & Lai) 1992;53:798–802*

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Single venous cannulation for valve operations (Robinson) 1992;53:365,CP

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Carcinoma, oat cell

Comparison between resected and irradiated small cell lung cancer in patients in stages I through IIIa (Ichinose, Hara, & others) 1992;53:95–100*

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Methylene blue guidance for simplified resection of a lung lesion (Kerrigan, Spence, & others) 1992;53:163–4,HW

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Inaccuracy of cardiac output by thermodilution during acute tricuspid regurgitation (Heerdt, Pond, & others) 1992;53: 706–8,CR

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Conjoined subrectus pocket for permanent pacemaker placement in the neonate (Ulicny, Detterbeck, & others) 1992; 53:1130–1,HW

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- Heart and unilateral lung transplantation for cardiomyopathy with high pulmonary vascular resistance (da Silva, Vila, & others) 1992;53:700–2,CR
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- Cardiac echinococcosis: cyst removal in a beating heart (Rossouw, Knott-Craig, & Erasmus) 1992;53:328–9,CR
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- Leukocyte activation with increased expression of CR3 receptors during cardiopulmonary bypass (Gu, van Oeveren, & others) 1992;53:839–43*
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- Warming during cardiopulmonary bypass is associated with jugular bulb desaturation (Croughwell, Frasco, & others) 1992;53:827–32*

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- Synchronous operation for ischemic cardiac and cerebrovascular disease: early results and long-term follow-up (Vermeulen, Ruben, others) 1992;53:381–90*

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- Acute pulmonary edema after Blalock-Taussig anastomosis (Okita, Miki, & others) 1992;53:684–5,CR
- Angiographic demonstration of no-flow anatomical patency of internal thoracic–coronary artery bypass grafts (Kitamura, Kawachi, & others) 1992;53:156–9,CR
- Aortic dissection without intimal rupture: diagnosis and management (Lui, Menkis, & McKenzie) 1992;53:886–8,CR
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- Benign schwannoma of the esophagus presenting as a giant fibrovascular polyp (Eberlein, Hannan, & others) 1992;53:343–5,CR
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Megaaorta and aortoiliac obstruction: alternate method of cannulation (Martin & Accola) 1992;53:889–91,CR

Mitral valve repair in patients on chronic hemodialysis (Sim, Mestres, & others) 1992;53:341–2,CR

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Pancoast syndrome: an unusual complication of pulmonary infection by *Staphylococcus aureus* (Gallagher, Jeffrey, & others) 1992;53:903–4,CR

Paraganglioma of the posterior mediastinum: value of magnetic resonance imaging (Tanaka, Kitano, & others) 1992;53:517–9,CR

Placement of a Greenfield filter in the superior vena cava (Owen, Schoettle, & Harrington) 1992;53:896–7,CR

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Successful treatment of acute postoperative pulmonary hypertension with nifedipine (Davis & Russo) 1992;53:148–50,CR

Surgical laser ablation of a pediatric idiopathic ventricular tachycardia (Nitta, Ikeshita, & others) 1992;53:692–3,CR

Systemic recombinant tissue plasminogen activator lysis for left atrial thrombus formation after single-lung retransplantation (Schmid, Gulba, & others) 1992;53:338–40,CR

Total anomalous pulmonary venous connection: surgical correction in a 66-year-old man (McMullan & Fyke) 1992;53:520–2,CR

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Unsuspected metastatic choriocarcinoma presenting as unilateral spontaneous pneumothorax (Ouelette & Inculet), 1992;53:144–5,CR

Catheterization

Retrograde cerebral perfusion through a superior vena caval cannula protects the brain (Usui, Hotta, & others) 1992;53:47–53*

Catheterization, Swan-Ganz

Severe endobronchial hemorrhage (Bonchek) 1992;53:739–40,CP; Reply (Smith & Scott) 1992;53:740,CP

Cells

Hemostatic abnormalities in total artificial heart patients as detected by specific blood markers (Walenga, Hoppensteadt, & others) 1992;53:844–50*

Central nervous system

Cyclosporine-associated central neurotoxicity after heart transplantation (McManus, O'Hair, & others) 1992;53:326–7,CR

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Warming during cardiopulmonary bypass is associated with jugular bulb desaturation (Croughwell, Frasco, & others) 1992;53:827–32*

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Surgical implications of transesophageal echocardiography to grade the atheromatous aortic arch (Ribakove, Katz, & others) 1992;53:758–63*

Synchronous operation for ischemic cardiac and cerebrovascular disease: early results and long-term follow-up (Vermeulen, Ruben, others) 1992;53:381–90*

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Iron chelation in myocardial preservation after ischemia-reperfusion injury: the importance of pretreatment and toxicity (DeBoer & Clark) 1992;53:412–8*

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"Provocative clamping" and removal of chest tubes despite persistent air leak (Kirschner) 1992;53:740–1,CP

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Adverse effect of prearrest hypothermia in immature hearts: rate versus duration of cooling (Hosseinzadeh, Tchervenkov, & others) 1992;53:464–71*

Aortico–right ventricular tunnel (Westaby & Archer) 1992;53:1107–9,CR

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Concomitant repair of aortopulmonary window and interrupted aortic arch (Ingram & Ott) 1992;53:909–11,HW

Conjoined subrectus pocket for permanent pacemaker placement in the neonate (Ulicny, Detterbeck, & others) 1992;53:1130–1,HW

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Breast development and areola sensitivity after submammary skin incision for median sternotomy (Deutinger & Domanig) 1992;53;1023–4*

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Surgical treatment of tricuspid regurgitation (Kay) 1992;53: 1132–3,CL

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Percutaneous localization of pulmonary nodules for thoracoscopic lung resection (Mack, Gordon, & others) 1992;53: 1123–4,HW

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Colorectal lung metastases: results of surgical excision (McAfee, Allen, & others) 1992;53:780–6*

Coronary aneurysm

Operative risks and long-term results of operation for left ventricular aneurysm (Komeda, David, & others) 1992;53: 22–9*

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Coronary artery operation in radiation-associated atherosclerosis: long-term follow-up (Hicks) 1992;53:670–4*

Saphenous-bicephalic aortocoronary graft in the treatment of right coronary bifurcation stenosis (Popoff, Saad, & Diaz) 1992;53:709–10,HW

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Angiographic demonstration of no-flow anatomical patency of internal thoracic–coronary artery bypass grafts (Kitamura, Kawachi, & others) 1992;53:156–9,CR

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Contraction and relaxation of human internal mammary artery after intraluminal administration of papaverine (Hillier, Watt, & others) 1992;53:1033–7*

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Coronary artery bypass (cont'd)
- Revascularization for coronary ostial stenosis in Takayasu's disease with calcified aorta (Tanaka, Abe, & others) 1992;53:894–5,CR
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Coronary thrombosis
- Systemic recombinant tissue plasminogen activator lysis for left atrial thrombus formation after single-lung retransplantation (Schmid, Gulba, & others) 1992;53:338–40,CR

Coronary vessels
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- Bronchoscopic appearance after single-lung transplantation (Eng, Sabanathan, & Newton) 1992;53:181–2,CP
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- Daniel A. Reid, MD: December 5, 1941–September 10, 1991 (Sommerhaug, Wolfe, & Lindsey) 1992;53:363,CP
- Emergency: an urgent problem emergent? (Hoffman) 1992;53:368,CP
- Esophagogastrectomy for acid injury (Ribet) 1992;53:739,CP
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  Response to heparinization in adults and children undergoing cardiac operations (Horkay, Martin, & others) 1992;53:822–6*
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  Cardiac function and myocardial performance of 24-hour–preserved asphyxiated canine hearts (Shirakura, Matsuda, & others) 1992;53:440–4*
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  - Fresh blood units contain large potent platelets that improve hemostasis after open heart operations (Mohr, Goor, & others) 1992;53:650–4*
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  - A lymphoid tumor obstructing the trachea in a child (Paç, Aydin, & Paç) 1992;53:548–9,CP
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  - Autologous fibrin glue from intraoperatively collected platelet-rich plasma (Oz, Jeevanandam, & others) 1992;53:530–1,HW
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  - Improved technique for hilar vascular stapling (Sugarbaker & Mentzer) 1992;53:165–6,HW
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  - Coronary bypass using arterial grafts in homozygous familial hypercholesterolemia (Takahashi, Nakano, & others) 1992;53:510–2,CR
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Immune tolerance
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  Cyclosporine-associated central neurotoxicity after heart transplantation (McManus, O'Hair, & others) 1992;53:326–7,CR
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  Effect of cardiopulmonary bypass on circulating lymphocyte function (Nguyen, Mulder, & Shennib) 1992;53:611–6*
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Interleukins
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Intestine, large
  Esophageal reconstruction for esophageal strictures or resection after corrosive injury (Wu & Lai) 1992;53:798–802*
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  Palliative intubation for dysphagia in patients with carcinoma of the esophagus (Liakakos, Ohri, & others) 1992;53:460–3*
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  Percutaneous replacement jejunostomy (Heitmiller, Venbrux, & Osterman) 1992;53:711–3,HW
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  Warming during cardiopulmonary bypass is associated with jugular bulb desaturation (Croughwell, Frasco, & others) 1992;53:827–32*

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  Benign tumors of the lung (Miller) 1992;53:179,KR
  Homograft replacement of the aortic valve (O'Brien) 1992;53:928–9,KR
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- Prolonged intraaortic balloon support for septal rupture after myocardial infarction (Estrada-Quintero, Uretsky, & others) 1992;53:335–7,CR

Myocardial reperfusion
- Analysis of determinants of ventricular fibrillation induced by reperfusion: dissociation between electrical instability and myocardial damage (Kinoshita, Mitani, & others) 1992;53: 999–1005*
- Myocardial protection by blood cardioplegia and warm reperfusion in heart transplantation (Nataf, Pavir, & others) 1992;53:525–6,HW

Myocardial reperfusion injury
- Activated neutrophils impair rabbit heart recovery after hypothermic global ischemia (Myers, Webb, & others) 1992;53: 247–52*
- Coronary artery endothelial cell and smooth muscle dysfunction after global myocardial ischemia (Dignan, Cornelius, & others) 1992;53:311–7*
- Efficacy of a hydroxyl radical scavenger (VF 233) in preventing reperfusion injury in the isolated rabbit heart (Ding, Dyke, & others) 1992;53:1091–5*
- Iron chelation in myocardial preservation after ischemia-reperfusion injury: the importance of pretreatment and toxicity (DeBoer & Clark) 1992;53:412–8*

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- Arthur Vineberg and the internal mammary artery implantation procedure (Dobell) 1992;53:167–9,CL
- Contraction and relaxation of human internal mammary artery after intraluminal administration of papaverine (Hillier, Watt, & others) 1992;53:1033–7*
- Coronary artery operation in radiation-associated atherosclerosis: long-term follow-up (Hicks) 1992;53:670–4*
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- Effect of internal mammary artery dissection on sternal vascularization (Carrier, Grégoire, & others) 1992;53:115–9*
- Harvesting of the internal mammary artery and the healing median sternotomy (Graeber) 1992;53:7–8,ED
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- The influence of age and sex on human internal mammary artery size and reactivity (Dignan, Yeh, & others) 1992;53: 792–7*
- Internal mammary artery preparation (Lewin) 1992;53:367–8,CP
- Open coronary endarterectomy, saphenous vein patch reconstruction, and internal mammary artery grafting (Lemma, Beretta, & others) 1992;53:1151–2,CP; Reply (Ladowski, Schatzlein, & Underhill) 1992;53:1152,CP
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  Systemic recombinant tissue plasminogen activator lysis for left atrial thrombus formation after single-lung retransplantation (Schmid, Gulba, & others) 1992;53:338–40,CR
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Herbert Sloan, MD

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Classified advertisements for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Art Carlucci, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010 (telephone: (212) 633-3806; facsimile: (212) 633-3820). All advertisements are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.50 per word per insertion, minimum 20 words.** Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of $18.00 per insertion for box number advertisements.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Advertisement orders should be for a maximum of 6 months; advertisements may be renewed for up to 6 months at a time. Advertisement copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Advertisements, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3853). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

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SITUATIONS AVAILABLE

Cardiothoracic and vascular surgeon, BE/BC, wanted to join a busy, well-established practice in Amarillo, Texas. Recent graduate preferred.

Please send CV to Henry E. Martinez, MD, 1901 Medi Park, Suite 1050, Amarillo, TX 79106; (806) 358-5108. 666B/G

Cardiovascular and thoracic surgeon, BE/BC, to expand new open heart program. Practice includes vascular and thoracic surgery. Located on the west coast of Florida. Send CV and references.

Please respond to Box 672. 672C/F

Thoracic, vascular surgeon, BE/BC wanted to join a well-established busy private group practice in Philadelphia area. Seek recent graduate. Excellent salary and benefits, leading to a full partnership. Please send curriculum vitae, clinical experience, and references.

Please respond to Box 680. 680C/H

Cardiothoracic surgeon, BE/BC, wanted to join 2 surgeons in busy and expanding practice on the West Coast. Experience or training in adult cardiac surgery, thoracic surgery, pacemaker surgery, valve repair, arrhythmia surgery, and thoracoscopy necessary. Position available July 1992; new or recent graduate preferred. Excellent salary and benefits with eventual partnership possible. Send curriculum vitae and references.

Please respond to Box 681. 681D/F

Cardiovascular surgeon: excellent practice opportunity for recently trained BC/BE to join a busy two-man practice in San Diego, California. Salary leading to full partnership.

Please send curriculum vitae to Medical Director, PO Box 28177, San Diego, CA 92128. 688D/F

Cardiothoracic surgeon: position for a fourth attending cardiothoracic surgeon available July 1992 in expanding multispecialty clinic practice. Candidate must be experienced in all aspects of adult cardiac and general thoracic surgery. Special expertise in thoracic aortic surgery desirable. No peripheral vascular surgery. Opportunity for resident teaching and clinical and laboratory research.

Respond with CV to David M. Shahian, MD, Chairman, Department of Thoracic and Cardiovascular Surgery, Lahey Clinic, 41 Mall Rd, PO Box 541, Burlington, MA 01805. EOE. 689D/F

Cardiovascular and thoracic surgeon: excellent opportunity for a board certified/eligible university-trained surgeon to join a new, growing department in a metropolitan New York community. Academic/private practice setting with excellent compensation. Experience in electrophysiologic surgery, artificial devices, and transplantation helpful. Please respond with curriculum vitae.

Please respond to Box 693. 693D/H

Cardiovascular and thoracic surgeon to join established 2-man private practice in Southeast. Practice includes cardiac and general thoracic surgery. Must be board certified or eligible in thoracic and cardiovascular surgery. Prefer candidate who has recently completed his/her training. Please respond with curriculum vitae.

Please respond to Box 696. 696E/J

Cardiothoracic surgeon needed for busy 6-surgeon group. Adult cardiac, thoracic, and peripheral vascular practice. Must be BE/BC. Generous salary and benefits leading to partnership.

Send CV to Jamal H. Khan, MD, Thoracic & Cardiovascular Associates, Inc, 3100 MacCorkle Ave, SE, Suite 411, Charleston, WV 25304. 698E/G

Assistant surgeon sought for busy adult cardiothoracic surgery practice. Entire responsibility will be to assist four senior surgeons in the operating room. Board certification or eligibility in general surgery, and some experience in vascular and/or thoracic surgery, desirable. Must be licensed in Pennsylvania or able to obtain license. Generous salary and fringes. Position is available immediately and could be permanent. Ideal location in very pleasant, small city near major eastern metropolitan centers.

Please respond with CV to Lawrence I. Bonchek, MD, 555 North Duke St, Lancaster, PA 17603; (717) 295-8395. 700E/F

Thoracic and cardiovascular surgeon with emphasis on pediatric/neonate cardiac surgery and cardiac transplantation is needed by a full-service thoracic and cardiovascular surgery group on the west coast. Must have ABTS certification. Excellent salary and benefits package. Please respond with curriculum vitae and case list.

Please respond to Box 702. 702E/J

Cardiovascular-thoracic surgeon, eligible or board certified, to join an established private practice in South Texas. Primary adult cardiac surgery with some thoracic and vascular surgery in modern hospital facilities.

Please send curriculum vitae to Filiberto Rodriguez, MD, 222 E Ridge Rd, Suite 101, McAllen, TX 78503. 704E/F

Cardiovascular/thoracic surgeon: a progressive major regional multispecialty group in Texas Gulf Coast area is seeking a BC/BE cardiovascular/thoracic surgeon. Applicant should be technically strong in all phases of adult cardiac surgery. Cardiology department has three cardiologists. Practice is located in subtropical climate in an upward bound economic environment. Guaranteed salary with bonus plan. Shareholder status available 12–18 months. Malpractice insurance, interview, and relocation expenses included in benefits package. Location is attractive to those who enjoy outdoor sports such as fishing, golfing, and sailing. Look into our great team!

Contact Amanda Fuhro, Valley Diagnostic Medical and Surgical Clinic, PA, 2200 Haine Dr, Harlingen, TX 78550; (512) 421-5199; 1(800) 852-4543. 709E/H

Outstanding opportunity available July 1 for recent graduate or no more than one year out of training in this new, rapidly growing adult cardiac surgery program. Practice also encompasses adult thoracic and vascular. Beautiful midwest location on lake. Respond with curriculum vitae.

Please respond to Box 715. 715E/F

Cardiac, thoracic, and peripheral vascular surgeon needed. Busy practice located in the Texas Gulf Coast area. Excellent location.

Please respond to Box 716. 716F/G

Cardiovascular and thoracic surgeon to join established three-man clinic practice in Arkansas. Practice includes thoracic, cardiac, and vascular surgery. Must be board eligible and board certified in thoracic and cardiovascular surgery.

Please send CV to Donald L. Patrick, MD, 1500 Dodson Ave, Fort Smith, AR 72901; (501-782-2071). 717F/K

Cardiothoracic/vascular surgeon: board certified in general and thoracic surgery. Minimum of 2 years of practice experience. Very active private multispecialty practice. Located in western Pennsylvania. Salary leading to full partnership. Excellent benefits. Detailed CV must accompany response. All replies treated confidentially.

Please respond to Box 719. 719F/K

Thoracic and vascular surgeon, BE/BC, to join active (noncardiac) thoracic and vascular practice in Pittsburgh, PA. Please respond with curriculum vitae and details of experience.

Please respond to Box 720. 720F/K

General thoracic surgeon: The Fox Chase Cancer Center, an NCI designated comprehensive cancer center, is seeking a board certified/board eligible thoracic surgeon to join an established program of thoracic surgical oncology. The successful candidate will have the opportunity to work in laboratory programs relating to lung cancer with nationally/internationally recognized experts in molecular biology, molecular cytogenetics, or radiation biology.

Mail letters of inquiry to Steven M. Keller, MD, Chief, Section of Thoracic Surgical Oncology, Fox Chase Cancer Center, 7701 Burholme Ave, Philadelphia, PA 19111. We are an equal opportunity employer. 721F

Thoracic and cardiovascular surgeon to join established private practice in NE Pennsylvania, board certified/eligible. Excellent benefit package and competitive salary leading to partnership.

Please respond with curriculum vitae and letter of reference to Richard J. Angelico, MD, 800 Ostrum St, Suite 303, Bethlehem, PA 18015; Fax number: (215) 954-3043. 722F

Cardiothoracic surgeon, board certified/eligible, wanted to join established practice in northwest Indiana (very near Chicago). Excellent salary. Please respond with curriculum vitae.

Please respond to Box 723. 723F/K

Faculty position as assistant professor of cardiothoracic surgery, skilled in clinical care of cardiac and noncardiac thoracic surgical patients. Must be interested in teaching and laboratory research and able to develop a research program with extramural funding. Send curriculum vitae, bibliography, and three letters of recommendation. The University of Pennsylvania is an equal opportunity/affirmative action employer.

Please respond to Box 724. 724F

The University of Pennsylvania Department of Surgery is seeking an individual at the professor/associate professor level to serve as Chief of the Division of Cardiothoracic Surgery. Candidates should be certified by the American Board of Thoracic Surgeons, have a record of outstanding clinical expertise and demonstrated skills in research, administration, and education.

Interested applicants should send CV to Brooke Roberts, MD, Chairman, Cardiothoracic Surgery Search Committee, Department of Surgery, 4 Silverstein, Hospital of the University of Pennsylvania, 34th & Spruce Streets, Philadelphia, PA 19104. An equal opportunity, affirmative action employer. 725F

Excellent opportunity in southern New England for recent graduate. ABTS certified or eligible cardiothoracic surgeon sought to join established group performing adult cardiothoracic and peripheral vascular surgery.

Please respond to Box 726. 726F/H

SITUATIONS WANTED

Cardiothoracic and vascular surgeon. Extensive experience. Wishes to relocate. Willing to assist or do surgery. Prefers Ventura, Oxnard, Santa Barbara, San Luis Obispo in southern California.

Please respond to Box 699. 699E/G

Fifty-five-year-old peripheral vascular surgeon with busy Midwest practice would like to slow down and relocate to the West Coast. Has 18 years' experience with vein harvesting and assisting at cardiac and thoracic surgery. Seeks similar position with established cardiothoracic group.

Please call (219) 233-5191. 711E/H

Cardiovascular and thoracic surgeon with extensive experience wishes to relocate. Trained in cardiac transplantation. Seeks opportunity with new program or group practice.

Please respond to Box 718. 718F/I

FELLOWSHIPS

Surgical residents/fellows—clinical residency/fellowship positions available in adult and pediatric cardiothoracic surgery. Large volume of cases. New Jersey license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart and Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015; (609) 893-6611, Ext 359. 653A/F

Cardiothoracic surgical fellowship—Allegheny General Hospital is seeking qualified candidates for a one-year, nonaccredited fellowship position in cardiothoracic surgery, available July 1, 1992, through June 30, 1993. The program enjoys a large volume of adult cardiac surgery and thoracic surgery cases, including thoracoscopy, esophageal and pulmonary resections, in addition to a strong research program. The program is assisted by seven physician assistants.

Please send CV and letters of recommendation to George J. Magovern, MD, Chairman, Department of Surgery, Allegheny General Hospital, 320 East North Ave, Pittsburgh, PA 15212; (412) 359-3715. 690D/G

1993 Annual Meeting of The Society of Thoracic Surgeons

The Twenty-ninth Annual Meeting will be held at the San Antonio Convention Center in San Antonio, Texas, January 25–27, 1993.

APPLICATION FOR MEMBERSHIP

(Deadline: September 1, 1992)

Requests for application forms for membership in The Society of Thoracic Surgeons should be addressed to Richard G. Sanderson, MD, Chairman, Membership Committee, The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611.

The completed application forms and supporting letters must be in the hands of the Membership Committee by **September 1, 1992,** for the applicant to be considered for election at the meeting in January 1993.

CALL FOR ABSTRACTS

(Deadline: August 17, 1992)

Abstracts for papers to be presented at the 1993 Annual Meeting are now being accepted. The deadline for receipt of abstracts is **August 17, 1992.** No papers *received* after this date will be accepted for inclusion in this year's program. An original and one copy should be submitted, using the official Society abstract form (on verso of this page), to Adnan Cobanoglu, MD, Timothy J. Gardner, MD, and Thomas W. Shields, MD, Co-Chairmen, Program Committee (Abstracts), The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611. Additional forms are available upon request from The Society. Abstracts must summarize an original contribution not presented or accepted for presentation elsewhere. Abstracts must be in the hands of the Program Committee by **August 17, 1992.** It is requested that the covering letter indicate the author who is to receive notice of acceptance or rejection **and** the author who will present the paper.

Abstracts may also be submitted for consideration in the Poster Session held in the exhibit area. Authors will be responsible for developing the poster presentation. Guidelines will be furnished.

The Thoracic Surgery Directors Association (TSDA) has established a Resident Presentation Award. Potential TSDA Resident Award abstracts must represent original work by the resident, who is to be first author and presenter. TSDA Resident Award abstracts may be directed to the regular Scientific Session or the Research Forum.

Essayists are reminded that according to the bylaws of The Society, all papers accepted for presentation: (1) must be submitted in *triplicate* to the Secretary at the time of presentation or to the Editor of *The Annals of Thoracic Surgery* prior to presentation; and (2) become the property of The Society if they are accepted for presentation.

It is well recognized that abstracts frequently belie their content by virtue of poor organization, and as a result valuable contributions to the Scientific Sessions may be unrecognized. It is important that methods and results be clearly defined in the abstract; therefore, general statements such as "results will be presented" are not acceptable. When a procedure or method is stated to have "advantages," those advantages should be defined. Abstracts that simply summarize results without defining objectives and methods are equally undesirable.

Speakers for accepted papers are limited to ten minutes.

Instructions for Abstracts

The official abstract form printed on verso of this page and available from The Society, or photocopies thereof, must be used. **Authors must categorize the principal subject of their abstract by checking the appropriate box.**

If the abstract should also be submitted for the Poster Session, please check the additional appropriate box.

If the author wishes to submit the abstract for consideration for the Thoracic Surgery Directors Association Award competition, the *additional* appropriate box must be checked. Also, the name of the Program Director must appear on a TSDA Resident Award abstract.

1. Full names of authors must appear on the abstract.
2. Institution or address is to be given, but omit titles, degrees, and appointments.
3. Abstracts must be limited to 250 words and must be typed double-spaced.
4. When percentages are used, the absolute numbers of derivation must be stated.
5. The body of the abstract should include:
   a. A brief statement of the purpose of the study being presented, with reference to the current state of research in the field.
   b. The methods of study or experimental approach clearly, but briefly, defined.
   c. A summary of the results and/or conclusions of the study, including sufficient details to support those conclusions.
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6. The form must be signed by the senior author attesting that the material will not be presented elsewhere if accepted for the scientific program nor published elsewhere if accepted for publication in *The Annals of Thoracic Surgery.*

In discussion of papers, The Society encourages a healthy spirit of constructive critical review and rebuttal by comments pertinent to the content of the paper being presented. Presentation of discussion in the form of "secondary papers" will not be welcomed.

CALL FOR SURGICAL FILMS OR VIDEO TAPES

(Deadline: August 3, 1992)

The popular Surgical Motion Picture program will again be presented at the Orlando meeting. The Program Committee hereby solicits the submission of surgical audiovisual presentations, which may portray a surgical procedure or simply a technical maneuver that the surgeon thinks will be of interest to The Society. The film (tape) may not exceed ten minutes in length. Sound is acceptable but not necessary; however, live narration by the principal surgeon is a requirement for participation in the movie night program. Presentations should be on 16-mm film, ¾-inch U-Matic video tape, or ½-inch VHS tape. The deadline for submission is **August 3, 1992.** Films and video tapes also should be sent to Adnan Cobanoglu, MD, Timothy J. Gardner, MD, and Thomas W. Shields, MD, Co-Chairmen, Program Committee, at The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611.

Richard P. Anderson, MD
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Information About Membership in The Society of Thoracic Surgeons

The Society of Thoracic Surgeons (STS) is the largest organization devoted primarily to the practice of thoracic and cardiovascular surgery. The major purpose of The Society is educational, with the aim of providing thoracic and cardiovascular surgeons from both academic and private practice environments a forum for presentation and discussion of scientific topics. As outlined in the original bylaws of The Society, this educational emphasis is designed to accomplish the broader goal of improving the quality and practice of thoracic and cardiovascular surgery as a specialty.

The STS recently held its 28th Annual Meeting. Since its founding in 1964, The Society has grown continually; the membership now includes the majority of board certified thoracic surgeons in the United States as well as thoracic and cardiovascular surgeons from 50 other countries.

In addition to holding an annual scientific meeting, the STS has more than 25 committees working on diverse matters related to improving thoracic and cardiovascular surgery as a specialty. Examples of these committees are: Standards and Ethics, Government Relations, Medico-Legal Affairs, Nomenclature and Coding, Education and Resources, Cardiothoracic Surgical Practice Guidelines, and Circulatory Support and Thoracic Transplantations. The Committee to Develop a National Database for Thoracic Surgery has implemented the first comprehensive database program for thoracic and cardiovascular surgeons in the United States; it is currently being offered to Society members.

There are five types of membership in The Society of Thoracic Surgeons: active, senior, honorary, international, and candidate.

Active Member Applicants for active membership must be surgeons whose practice is devoted primarily to the field of thoracic and cardiovascular surgery.

QUALIFICATIONS: Applicants must be Diplomates of the American Board of Thoracic Surgery or Fellows in The Royal College of Surgeons of Canada, and be established in the practice of thoracic and/or cardiovascular surgery for a minimum of 3 years. There must be sponsoring letters from three active STS members.

Senior Member Any active member or international member, upon reaching the age of 65 years, shall automatically become a Senior Member.

Honorary Member Honorary membership shall be reserved for distinguished persons worldwide who have achieved prominence in the field of thoracic and cardiovascular surgery and have contributed to its advancement. Honorary members shall be elected by a majority vote of The Society at its annual business session upon recommendation of the Council of the STS.

International Member Members from countries other than the United States and Canada were previously accepted only as active members. Because of differences in training and practice, the application process for foreign members was often complex and time consuming. To allow for greater international participation, the bylaws were revised to provide for the category of international member.

QUALIFICATIONS: Applicants shall reside outside the United States and Canada. They shall have completed training equivalent to that required for active membership. They shall have achieved appropriate certification or recognition of achievement in the specialty in their country and must devote the majority of their professional efforts to the interests of the specialty. Appropriate documentation of professional achievements shall be provided to the Membership Committee.

Candidate Member The candidate membership category was created to allow participation of younger surgeons not yet qualified for active membership.

QUALIFICATIONS: Applicants shall be enrolled in a thoracic and cardiovascular training program accredited by the Residency Review Committee for Thoracic Surgery under the authority of the Accreditation Council for Graduate Medical Education or in a training program similarly approved by The Royal College of Surgeons of Canada. Also, individuals who have completed their training in one of the above programs and are in process of acquiring certification or have been certified by the American Board of Thoracic Surgery or The Royal College of Surgeons of Canada and are awaiting fulfillment of the 3-year residence requirement for active membership are eligible for this type of membership.

If you would like to receive an application for membership in The Society, send the request printed below. This year's deadline for receipt of applications is September 1, 1992. We suggest you apply soon as it takes time to process the application. Approved applications will be presented to the membership at the January 1993 Annual Meeting in San Antonio, TX.

REQUEST FOR APPLICATIONS

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TO: NAME: ________________________

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Send to: Richard G. Sanderson, MD, Chairman, Membership Committee
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The Cleveland Clinic Foundation
Department of Thoracic and Cardiovascular Surgery
Desk F - 25
Education Coordinator, Laura L. Cotton
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216-445-6816

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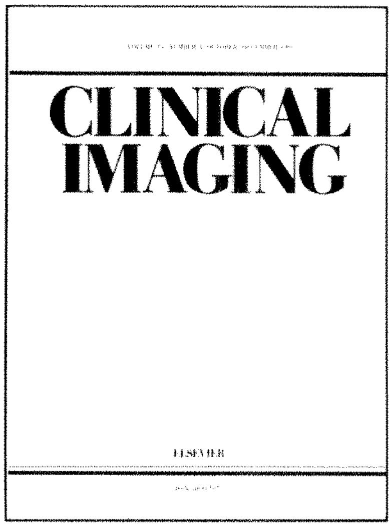

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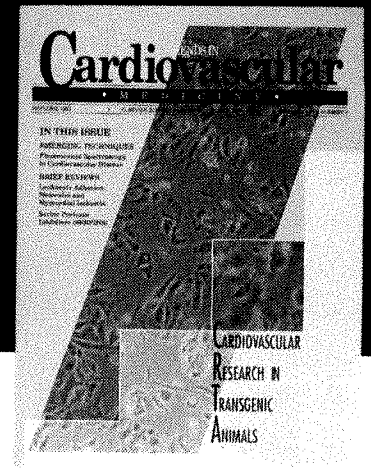

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EVENTS OF INTEREST

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■ Thirty-eighth Annual Meeting of the American Society for Artificial Internal Organs, Nashville, Tennessee—May 7–9, 1992

For information on this meeting, contact ASAIO Registration, 2200 North Federal Highway, Suite 201, Boca Raton, FL 33431-7710.

■ Fourteenth World Congress of The International Society for Heart Research, Kobe, Japan—May 10–14, 1992

For information on this meeting, contact Makoto Nagano, MD, Secretariat, XIV World Congress of ISHR, Department of Internal Medicine, Jikel University Medical School, Aoto Hospital, 6-41-2 Aoto, Katsushika-ku, Tokyo 125, Japan.

■ Aortic Surgery 1992: State of the Art, Boston, Massachusetts—May 14–15, 1992

For information on this meeting, contact Harvard MED-CME, PO Box 825, Boston, MA 02117; or telephone (617) 432-1525.

■ Innovative Surgical Approaches to Acquired Heart Disease, Toronto, Canada—June 5–6, 1992

For information on this live teleconference, contact Margo Irr, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

■ The International Society for Cardiovascular Surgery/The Society for Vascular Surgery, Chicago, Illinois—June 8–10, 1992

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ Cardiostim 92, Nice, France—June 17–20, 1992

For information on this meeting, contact Dr J. Mugica, Centre Chirurgical Val d'Or, 16, rue Pasteur, 92211 St-Cloud Cedex, France; or telephone (33) 1.46.02.70.72 (facsimile: (33) 1.46.02.05.09).

■ Eighteenth Annual Meeting of The Western Thoracic Surgical Association, Kauai, Hawaii—June 25–27, 1992

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■ Surgery of the Airways, Boston, Massachusetts—July 20–21, 1992

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■ Contemporary Techniques for Aortic Valve Surgery: Homograft, Autograft, and Stentless Valve Implantation, Sardinia, Italy—August 24–29, 1992

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■ Sixth Annual Meeting of the European Society for Vascular Surgery, Athens, Greece—September 2–4, 1992

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■ American College of Surgeons, New Orleans, Louisiana—October 11–16, 1992

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050 (facsimile: (312) 440-7014).

■ Concepts in Myocardial Revascularisation, Leicester, United Kingdom—October 15–16, 1992

For information on this international symposium, contact Mrs Fiona Legate, Department of Cardiology, Glenfield General Hospital, Groby Rd, Leicester, UK; or telephone (44) 533-871471, ext 3038 (facsimile: (44) 533-875792).

■ Myocardial Preservation: Past Trends and Future Technology, Atlanta, Georgia—October 16–17, 1992

For information on this meeting, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

■ Fifty-eighth Annual Scientific Assembly, American College of Chest Physicians, Chicago, Illinois—October 25–29, 1992

For information on this meeting, contact American College of Chest Physicians, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ Thirty-ninth Annual Meeting of the Southern Thoracic Surgical Association, Wesley Chapel (near Tampa), Florida—November 5–7, 1992

For information on this meeting, contact Southern Thoracic Surgical Association, 401 N Michigan Ave, Chicago, IL 60611-4267; or telephone (312) 644-6610 (facsimile: (312) 321-6869).

■ Sixty-fifth Scientific Session of the American Heart Association, New Orleans, Louisiana—November 16–19, 1992

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 373-6300 (facsimile: (214) 373-3406).

■ Le Club Mitrale—Live Teleconference, Paris, France—December 7–9, 1992

For information on this meeting, contact Lisa Turnbull, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

■ Twenty-ninth Annual Meeting of The Society of Thoracic Surgeons, San Antonio, Texas—January 25–27, 1993

For information on this meeting, contact Richard P. Anderson, MD, The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611; or telephone (312) 644-6610.

■ Third World Congress of the International Society of Cardio-Thoracic Surgeons, Salzburg, Austria—January 25–27, 1993

For information on this meeting, contact Prof Dr Felix Unger, c/o Interconvention, Austria Center Vienna, A-1450 Vienna, Austria; or telephone +43/1/23 69-26 43 (facsimile: +43/1/23 69-648).

■ Forty-second Annual Meeting of the American College of Cardiology, Anaheim, California—March 14–18, 1993

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone (800) 253-4636.

■ One Hundred Thirteenth Annual Meeting of the American Surgical Association, Baltimore, Maryland—April 1–3, 1993

For information on this meeting, contact American Surgical Association, Department of Surgery, CB 7245, University of North Carolina, 136 Burnett-Womack Building, Chapel Hill, NC 27599; or telephone (919) 966-4320 (facsimile: (919) 966-6009).

■ Seventy-third Annual Meeting of the American Association for Thoracic Surgery, Chicago, Illinois—April 26–28, 1993

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ World Congress on Diseases of the Chest, Amsterdam, the Netherlands—June 13–18, 1993

For information on this meeting, contact XVII World Congress on Diseases of the Chest, International Academy of Chest Physicians & Surgeons, 3300 Dundee Rd, Northbrook, IL 60062-2348.

CLASSIFIED ADVERTISEMENTS

Classified advertisements for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Art Carlucci, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010 (telephone: (212) 633-3806; facsimile: (212) 633-3820). All advertisements are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.50 per word per insertion, minimum 20 words.** Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of $18.00 per insertion for box number advertisements.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Advertisement orders should be for a maximum of 6 months; advertisements may be renewed for up to 6 months at a time. Advertisement copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery,* Desk Editorial, Classified Advertisements, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3853). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

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SITUATIONS AVAILABLE

Cardiothoracic and vascular surgeon, board eligible or certified, to join 2-man private practice in Ft. Lauderdale, Florida. Send CV.

Please respond to Box 542. 542L/E

Cardiothoracic surgeon, BE/BC, wanted to join established practice in mid-Michigan group of two. Ninety percent of practice is adult surgery and ten percent is general thoracic surgery. Respond with CV and names of references.

Please respond to Box 644. 644L/E

Thoracic surgeon wanted: a busy general thoracic surgical practice (non–open-heart, nonvascular) 20 miles south of Boston seeks to add a third surgeon. Candidate must be board certified or eligible. This active practice operates from a multihospital referral base. The community is an ideal area for family living, with excellent schools and nearby Boston and Cape Cod cultural and recreational facilities. Competitive salary, malpractice insurance, and excellent benefits package. Please respond with CV.

Please respond to Box 648. 648L/E

Cardiovascular and thoracic surgeon, BC/BE, to join a three-man established expanding private practice in central Florida. Excellent salary and fringe benefits package leading to partnership.

Please respond with CV to Wayne McGraw, PO Box 3130, Ocala, FL 32678; (904) 867-8311. 665B/D

Cardiothoracic and vascular surgeon, BE/BC, wanted to join a busy, well-established practice in Amarillo, Texas. Recent graduate preferred.

Please send CV to Henry E. Martinez, MD, 1901 Medi Park, Suite 1050, Amarillo, TX 79106; (806) 358-5108. 666B/G

Thoracic/cardiovascular surgeon: three-man group in suburban New York doing general thoracic and peripheral vascular surgery desires new graduate of approved thoracic program with training in vascular surgery. Please respond with CV.

Please respond to Box 671. 671C/E

Cardiovascular and thoracic surgeon, BE/BC, to expand new open heart program. Practice includes vascular and thoracic surgery. Located on the west coast of Florida. Send CV and references.

Please respond to Box 672. 672C/F

Cardiothoracic surgeon wanted for July 1992: Expanding private practice in Philadelphia. Adult cardiac and thoracic surgery. Academic appointment. Eventual partnership.

Send CV and references to PO Box 1295, Philadelphia, PA 19105. 674C/E

Wanted: vascular or thoracic/vascular surgeon. Join two others in New England private practice. Prefer recent graduate.

Please respond to Box 677. 677C/D

Thoracic, vascular surgeon, BE/BC wanted to join a well-established busy private group practice in Philadelphia area. Seek recent graduate. Excellent salary and benefits, leading to a full partnership. Please send curriculum vitae, clinical experience, and references.

Please respond to Box 680. 680C/H

Cardiothoracic surgeon, BE/BC, wanted to join 2 surgeons in busy and expanding practice on the West Coast. Experience or training in adult cardiac surgery, thoracic surgery, pacemaker surgery, valve repair, arrhythmia surgery, and thoracoscopy necessary. Position available July 1992; new or recent graduate preferred. Excellent salary and benefits with eventual partnership possible. Send curriculum vitae and references.

Please respond to Box 681. 681D/F

BC/BE cardiothoracic surgeon wanted to join active adult cardiothoracic surgery practice in the Midwest. Reply with CV.

Please respond to Box 682. 682D

Cardiovascular surgeon wanted to join two cardiovascular surgeons in busy private setting. Practice is based in a modern, well-equipped teaching hospital in the Midwest. Primary interest should be cardiac surgery. A recent graduate with strong academic background is desired. Please respond with curriculum vitae.

Please respond to Box 684. 684D/E

Cardiovascular surgeon: excellent practice opportunity for recently trained BC/BE to join a busy two-man practice in San Diego, California. Salary leading to full partnership.

Please send curriculum vitae to Medical Director, PO Box 28177, San Diego, CA 92128. 688D/F

Cardiothoracic surgeon: position for a fourth attending cardiothoracic surgeon available July 1992 in expanding multispecialty clinic practice. Candidate must be experienced in all aspects of adult cardiac and general thoracic surgery. Special expertise in thoracic aortic surgery desirable. No peripheral vascular surgery. Opportunity for resident teaching and clinical and laboratory research.

Respond with CV to David M. Shahian, MD, Chairman, Department of Thoracic and Cardiovascular Surgery, Lahey Clinic, 41 Mall Rd, PO Box 541, Burlington, MA 01805. EOE. 689D/F

Cardiothoracic and vascular surgeon, to join a busy and well-established three-man practice in the Midwest. Applicant should be board certified or eligible in thoracic and cardiovascular surgery. Competitive salary leading to partnership. Please respond with CV.

[illegible] spond to Box 691. 691D

Cardiovascular and thoracic surgeon: excellent opportunity for a board certified/eligible university-trained surgeon to join a new, growing department in a metropolitan New York community. Academic/private practice setting with excellent compensation. Experience in electrophysiologic surgery, artificial devices, and transplantation helpful. Please respond with curriculum vitae.

Please respond to Box 693. 693D/H

Research associate in cardiovascular surgery: to work in established, productive, experimental surgery laboratory. Projects in temporary and permanent left ventricular assist systems and related artificial organs. Opportunity to participate in clinical research. Clinical open heart surgery experience essential; investigative background preferred. Send curriculum vitae and selected publications.

Please respond to Box 694. 694D

SITUATIONS WANTED

Intensivist: 39-year-old fellowship-trained, board certified in critical care medicine, FCCM. Eight years Director of surgical ICU in an academic environment managing cardiac, vascular, multiple trauma, and other surgery patients. Research, publications, awards. Skilled in all invasive ICU procedures: ventilators, PA catheters, bronchoscopy, hemofiltration, pacing, etc. Seek directorship of cardiac surgical ICU, general surgical ICU, or mixed medical/surgical ICU. Prefer proximity to a metropolitan area with cultural amenities.

Please respond to Box 676. 676C/D

B/C surgeon seeking thoracic surgery fellowship, preferably leading to certification by the ABTS.

Please respond to Box 685. 685D

Middle-aged, fully certified thoracic and cardiovascular surgeon with 15 years of active, independent, and successful private practice seeks part-time position as surgical assistant and chart rounder in the southeast US including Florida.

Please respond to Box 686. 686D

Cardiac surgeon: US graduate, ABS, ABTS, 10 years practice, geographically isolated, low-volume program, excellent mortality, seeks relocation to potential high-volume group practice setting.

Please respond to Box 687. 687D

FELLOWSHIPS

Surgical residents/fellows—clinical residency/fellowship positions available in adult and pediatric cardiothoracic surgery. Large volume of cases. New Jersey license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart and Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015; (609) 893-6611, Ext 359. 653A/D

One-year fellowship in cardiothoracic surgery available. Excellent educational experience with good compensation. Board certified and/or eligible in general surgery preferred but not required.

Please respond to Box 683. 683D

Cardiothoracic surgical fellowship—Allegheny General Hospital is seeking qualified candidates for a one-year, nonaccredited fellowship position in cardiothoracic surgery, available July 1, 1992, through June 30, 1993. The program enjoys a large volume of adult cardiac surgery and thoracic surgery cases, including thoracoscopy, esophageal and pulmonary resections, in addition to a strong research program. The program is assisted by seven physician assistants.

Please send CV and letters of recommendation to George J. Magovern, MD, Chairman, Department of Surgery, Allegheny General Hospital, 320 East North Ave, Pittsburgh, PA 15212; (412) 359-3715. 690D/G

Heart/lung transplant fellow—for July 1, 1992. One-year medical/surgical fellowship in heart/lung transplantation. Our center evaluates over 100 patients annually and follows more than 150 preoperative and postoperative patients yearly.

Contact Robert M. Mentzer, Jr, MD, Division of Cardiothoracic Surgery, University of Wisconsin Hospitals and Clinics, 600 Highland Ave, Madison, WI 53792. 692D

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A one year fellowship beginning July 1, 1992, is available for a board eligible or certified cardiothoracic surgeon seeking additional training in general thoracic surgery. This one year program includes all aspects of general thoracic surgery with an extensive commitment to surgery of the esophagus and pulmonary transplantation. The service performs over 800 procedures yearly with 450 major operations. For information please contact: **Thomas W. Rice, M.D.**

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St. Luke's Episcopal Hospital currently has opportunities available for fellowship in transplantation. St. Luke's is affiliated with The Texas Heart Institute, and located at the Texas Medical Center in Houston. Fellowship responsibilities include extensive exposure to all aspects of mechanical circulatory support, including intra-aortic balloon pump, centrifugal, pneumatic and electrical left ventricular assist devices. In addition, there are excellent opportunities for clinical and animal research. Graduation from an accredited medical school plus two years' general surgery training are required. Please send your current resume to our Employment Office (4-293), P.O. Box 20269, Houston, Texas 77225-0269.

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Hovald K. Helseth, M.D., Chief
Division of Cardiothoracic Surgery
Department of Surgery
Hennepin County Medical Center
Minneapolis, MN 55415

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(803) 449-4411, ext. 1380, 1381

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(214) 661-4866

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Edward Verrier, M.D.
University of Washington
Department of Surgery, SA-25
1959 Northeast Pacific Street
Seattle, WA 98195
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Medical Director
Carle Clinic Association
602 West University, Urbana, Illinois 61801
call collect (217) 383-3399, FAX (217) 383-3163

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EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

■ Innovative Surgical Approaches to Acquired Heart Disease, Toronto, Canada—June 5–6, 1992

For information on this live teleconference, contact Margo Irr, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

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For information on this meeting, contact Congress Secretariat, RCT asociados, Aulèstia i Pijoan, 12, 08012 Barcelona, Spain; or telephone 34-3-4156938 (facsimile: 34-3-4156904).

■ American College of Surgeons, New Orleans, Louisiana—October 11–16, 1992

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050 (facsimile: (312) 440-7014).

■ Concepts in Myocardial Revascularisation, Leicester, United Kingdom—October 15–16, 1992

For information on this international symposium, contact Mrs Fiona

Legate, Department of Cardiology, Glenfield General Hospital, Groby Rd, Leicester, UK; or telephone (44) 533-871471, ext 3038 (facsimile: (44) 533-875792).

■ Myocardial Preservation: Past Trends and Future Technology, Atlanta, Georgia—October 16–17, 1992

For information on this meeting, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

■ Fifty-eighth Annual Scientific Assembly, American College of Chest Physicians, Chicago, Illinois—October 25–29, 1992

For information on this meeting, contact American College of Chest Physicians, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ Thirty-ninth Annual Meeting of the Southern Thoracic Surgical Association, Wesley Chapel (near Tampa), Florida—November 5–7, 1992

For information on this meeting, contact Southern Thoracic Surgical Association, 401 N Michigan Ave, Chicago, IL 60611-4267; or telephone (312) 644-6610 (facsimile: (312) 321-6869).

■ Cardiac Surgery 1993: State of the Art, St. Thomas, US Virgin Islands—November 12–14, 1992

The fifth annual conference for cardiac surgeons, perfusionists, nurses, and allied health personnel is sponsored by the Academy of Medicine of New Jersey and Cooper Hospital/University Medical Center, UMDNJ-Robert Wood Johnson Medical School at Camden. For further information, contact Rosemary Morrone: (609) 963-3757.

■ Sixty-fifth Scientific Session of the American Heart Association, New Orleans, Louisiana—November 16–19, 1992

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 373-6300 (facsimile: (214) 373-3406).

■ Le Club Mitrale—Live Teleconference, Paris, France—December 7–9, 1992

For information on this meeting, contact Lisa Turnbull, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

■ Twenty-ninth Annual Meeting of The Society of Thoracic Surgeons, San Antonio, Texas—January 25–27, 1993

For information on this meeting, contact Richard P. Anderson, MD, The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611; or telephone (312) 644-6610.

■ Third World Congress of the International Society of Cardio-Thoracic Surgeons, Salzburg, Austria—January 25–27, 1993

For information on this meeting, contact Prof Dr Felix Unger, c/o Interconvention, Austria Center Vienna, A-1450 Vienna, Austria; or telephone +43/1/23 69-26 43 (facsimile: +43/1/23 69-648).

■ Forty-second Annual Meeting of the American College of Cardiology, Anaheim, California—March 14–18, 1993

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone (800) 253-4636.

■ One Hundred Thirteenth Annual Meeting of the American Surgical Association, Baltimore, Maryland—April 1–3, 1993

For information on this meeting, contact American Surgical Association, Department of Surgery, CB 7245, University of North Carolina, 136 Burnett-Womack Building, Chapel Hill, NC 27599; or telephone (919) 966-4320 (facsimile: (919) 966-6009).

■ Seventy-third Annual Meeting of the American Association for Thoracic Surgery, Chicago, Illinois—April 26–28, 1993

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ World Congress on Diseases of the Chest, Amsterdam, the Netherlands—June 13–18, 1993

For information on this meeting, contact XVII World Congress on Diseases of the Chest, International Academy of Chest Physicians & Surgeons, 3300 Dundee Rd, Northbrook, IL 60062-2348.

CLASSIFIED ADVERTISEMENTS

Classified advertisements for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Art Carlucci, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010 (telephone: (212) 633-3806; facsimile: (212) 633-3820). All advertisements are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.50 per word per insertion, minimum 20 words.** Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of $18.00 per insertion for box number advertisements.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Advertisement orders should be for a maximum of 6 months; advertisements may be renewed for up to 6 months at a time. Advertisement copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Advertisements, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3853). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

Please note that *The Annals* does not function as a placement service and cannot provide information on advertised positions. When answering advertisements, please write individually to each advertiser you wish to contact, using the address given in the advertisement. To respond to an anonymous advertisement, write to Box Number, *The Annals of Thoracic Surgery*, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

SITUATIONS AVAILABLE

Cardiothoracic and vascular surgeon, board eligible or certified, to join 2-man private practice in Ft. Lauderdale, Florida. Send CV.

Please respond to Box 542. 542L/E

Cardiothoracic surgeon, BE/BC, wanted to join established practice in mid-Michigan group of two. Ninety percent of practice is adult surgery and ten percent is general thoracic surgery. Respond with CV and names of references.

Please respond to Box 644. 644L/E

Thoracic surgeon wanted: a busy general thoracic surgical practice (non–open-heart, nonvascular) 20 miles south of Boston seeks to add a third surgeon. Candidate must be board certified or eligible. This active practice operates from a multihospital referral base. The community is an ideal area for family living, with excellent schools and nearby Boston and Cape Cod cultural and recreational facilities. Competitive salary, malpractice insurance, and excellent benefits package. Please respond with CV.

Please respond to Box 648. 648L/E

Cardiothoracic and vascular surgeon, BE/BC, wanted to join a busy, well-established practice in Amarillo, Texas. Recent graduate preferred.

Please send CV to Henry E. Martinez, MD, 1901 Medi Park, Suite 1050, Amarillo, TX 79106; (806) 358-5108. 666B/G

Thoracic/cardiovascular surgeon: three-man group in suburban New York doing general thoracic and peripheral vascular surgery desires new graduate of approved thoracic program with training in vascular surgery. Please respond with CV.

Please respond to Box 671. 671C/E

Cardiovascular and thoracic surgeon, BE/BC, to expand new open heart program. Practice includes vascular and thoracic surgery. Located on the west coast of Florida. Send CV and references.

Please respond to Box 672. 672C/F

Cardiothoracic surgeon wanted for July 1992: Expanding private practice in Philadelphia. Adult cardiac and thoracic surgery. Academic appointment. Eventual partnership.

Send CV and references to PO Box 1295, Philadelphia, PA 19105. 674C/E

Thoracic, vascular surgeon, BE/BC wanted to join a well-established busy private group practice in Philadelphia area. Seek recent graduate. Excellent salary and benefits, leading to a full partnership. Please send curriculum vitae, clinical experience, and references.

Please respond to Box 680. 680C/H

Cardiothoracic surgeon, BE/BC, wanted to join 2 surgeons in busy and expanding practice on the West Coast. Experience or training in adult cardiac surgery, thoracic surgery, pacemaker surgery, valve repair, arrhythmia surgery, and thoracoscopy necessary. Position available July 1992; new or recent graduate preferred. Excellent salary and benefits with eventual partnership possible. Send curriculum vitae and references.

Please respond to Box 681. 681D/F

Cardiovascular surgeon wanted to join two cardiovascular surgeons in busy private setting. Practice is based in a modern, well-equipped teaching hospital in the Midwest. Primary interest should be cardiac surgery. A recent graduate with strong academic background is desired. Please respond with curriculum vitae.

Please respond to Box 684. 684D/E

Cardiovascular surgeon: excellent practice opportunity for recently trained BC/BE to join a busy two-man practice in San Diego, California. Salary leading to full partnership.

Please send curriculum vitae to Medical Director, PO Box 28177, San Diego, CA 92128. 688D/F

Cardiothoracic surgeon: position for a fourth attending cardiothoracic surgeon available July 1992 in expanding multispecialty clinic practice. Candidate must be experienced in all aspects of adult cardiac and general thoracic surgery. Special expertise in thoracic aortic surgery desirable. No peripheral vascular surgery. Opportunity for resident teaching and clinical and laboratory research.

Respond with CV to David M. Shahian, MD, Chairman, Department of Thoracic and Cardiovascular Surgery, Lahey Clinic, 41 Mall Rd, PO Box 541, Burlington, MA 01805. EOE. 689D/F

Cardiovascular and thoracic surgeon: excellent opportunity for a board certified/eligible university-trained surgeon to join a new, growing department in a metropolitan New York community. Academic/private practice setting with excellent compensation.

Experience in electrophysiologic surgery, artificial devices, and transplantation helpful. Please respond with curriculum vitae.

Please respond to Box 693. 693D/H

Cardiothoracic surgeon, BC/BE, to practice general thoracic and cardiac surgery with the Burns Clinic Medical Center, a 110-physician multispecialty group. You would be joining two other cardiothoracic surgeons and six cardiologists. Our comprehensive benefit package includes up to a two-year guaranteed base salary; vacation/meeting time; sabbatical leave; dental, health, and life insurance; professional liability; disability insurance; membership dues and meeting expenses; pension and profit sharing plans; and shareholder status after two years. Located on the shores of Lake Michigan, the area offers four seasons of spectacular scenic beauty, sports, cultural and recreational activities.

For more information send CV to Linda Curtiss, Recruitment Coordinator, c/o Burns Clinic Medical Center, 560 W Mitchell, Petoskey, MI 49770; (616) 348-6504. 695E

Cardiovascular and thoracic surgeon to join established 2-man private practice in Southeast. Practice includes cardiac and general thoracic surgery. Must be board certified or eligible in thoracic and cardiovascular surgery. Prefer candidate who has recently completed his/her training. Please respond with curriculum vitae.

Please respond to Box 696. 696E/J

Cardiothoracic surgeon needed for busy 6-surgeon group. Adult cardiac, thoracic, and peripheral vascular practice. Must be BE/BC. Generous salary and benefits leading to partnership.

Send CV to Jamal H. Khan, MD, Thoracic & Cardiovascular Associates, Inc, 3100 MacCorkle Ave, SE, Suite 411, Charleston, WV 25304. 698E/G

Assistant surgeon sought for busy adult cardiothoracic surgery practice. Entire responsibility will be to assist four senior surgeons in the operating room. Board certification or eligibility in general surgery, and some experience in vascular and/or thoracic surgery, desirable. Must be licensed in Pennsylvania or able to obtain license. Generous salary and fringes. Position is available immediately and could be permanent. Ideal location in very pleasant, small city near major eastern metropolitan centers.

Please respond with CV to Lawrence I. Bonchek, MD, 555 North Duke St, Lancaster, PA 17603; (717) 295-8395. 700E/F

University of Florida seeks cardiovascular surgeon to join major teaching unit in Jacksonville, Florida, at University Medical Center. Candidate should be board eligible/certified in thoracic surgery. We seek someone with strong research and teaching interests with clinical experience in cardiac transplantation. Position is tenure-accruing with academic appointment at Assistant to Associate Professor level, depending upon qualifications. Applicant recruiting deadline: June 1, 1992.

Forward curriculum vitae and names/addresses of three references to Eric Ceithaml, MD, Chairman, Cardiovascular Search Committee, University Medical Center, 655 West 8th St, Jacksonville, FL 32209. Affirmative action/equal employment opportunity employer. 701E

Thoracic and cardiovascular surgeon with emphasis on pediatric/neonate cardiac surgery and cardiac transplantation is needed by a full-service thoracic and cardiovascular surgery group on the west coast. Must have ABTS certification. Excellent salary and benefits package. Please respond with curriculum vitae and case list.

Please respond to Box 702. 702E/J

Cardiovascular-thoracic surgeon, eligible or board certified, to join an established private practice in South Texas. Primary adult cardiac surgery with some thoracic and vascular surgery in modern hospital facilities.

Please send curriculum vitae to Filiberto Rodriguez, MD, 222 E Ridge Rd, Suite 101, McAllen, TX 78503. 704E/F

Thoracic surgeon: Position available for board certified or eligible academic thoracic surgeon at Harvard Medical School/Brigham & Women's Hospital-affiliated Boston area VA Medical Center. Active research programs. Responsible for thoracic noncardiac program with opportunity to perform variable amount of cardiac surgery.

Interested candidates should forward CV to Shukri F. Khuri, MD, Chief of Surgery, West Roxbury VA Medical Center, 1400 VFW Parkway, West Roxbury, MA 02132. 705E

Physician's assistant—cardiothoracic surgery, position available in our university-affiliated hospital. Individual will be providing clinical support to the Chief of Cardiothoracic Surgery, including all preoperative, perioperative, and postoperative aspects of care. NYS licensure required or readily obtainable.

Please send CV to C. E. Anagnostopoulos, MD, Chief, Division of Cardiothoracic Surgery, c/o Marylee Davis, Human Resources, St. Luke's/Roosevelt Hospital Center, 114th St and Amsterdam Ave, NY, NY 10025; (212) 523-1611. EOE M/F. 706E

Assistant/associate professor—needed for new full-time cardiothoracic surgery program in our university hospital affiliated with Columbia University. Position involves primarily adult cardiac surgery with some thoracic. Successful candidate must be ABTS and NYS licensure eligible, have experience in areas of acquired heart disease, and possess a strong commitment to research and teaching.

Please send CV to C. E. Anagnostopoulos, MD, Chief, Division of Cardiothoracic Surgery, c/o Marylee Davis, Human Resources, St. Luke's/Roosevelt Hospital Center, 114th St and Amsterdam Ave, NY, NY 10025. EOE M/F. 708E

Cardiovascular/thoracic surgeon: a progressive major regional multispecialty group in Texas Gulf Coast area is seeking a BC/BE cardiovascular/thoracic surgeon. Applicant should be technically strong in all phases of adult cardiac surgery. Cardiology department has three cardiologists. Practice is located in subtropical climate in an upward bound economic environment. Guaranteed salary with bonus plan. Shareholder status available 12–18 months. Malpractice insurance, interview, and relocation expenses included in benefits package. Location is attractive to those who enjoy outdoor sports such as fishing, golfing, and sailing. Look into our great team!

Contact Amanda Fuhro, Valley Diagnostic Medical and Surgical Clinic, PA, 2200 Haine Dr, Harlingen, TX 78550; (512) 421-5199; 1(800) 852-4543. 709E/H

Cardiothoracic surgeon: busy cardiothoracic surgeon seeking an associate to join established, rapidly growing practice in North Florida. Excellent opportunity, unparalleled living and working environment.

Please respond to Box 710. 710E

Wanted: clinical instructor in the Division of Cardiothoracic Surgery. Duties include clinical, teaching, and research endeavors in the field of cardiothoracic surgery. Qualifications: board certified in general surgery and board certified or eligible in thoracic surgery.

Send resume to Division of Cardiothoracic Surgery, University of Missouri-Columbia, One Hospital Dr, Columbia, MO 65212. Application deadline is June 1, 1991. The University of Missouri-Columbia is an equal opportunity and affirmative action institution. 713E

Wanted: assistant/associate professor in the Division of Cardiothoracic Surgery. Duties include teaching, research, operative

responsibilities in adult cardiac surgery and in general thoracic surgery. Qualifications: board certified in general surgery and board certified or eligible in thoracic surgery.

Send resume to Division of Cardiothoracic Surgery, University of Missouri-Columbia, One Hospital Dr, Columbia, MO 65212. Application deadline is June 1, 1991. The University of Missouri-Columbia is an equal opportunity and affirmative action institution. 714E

Outstanding opportunity available July 1 for recent graduate or no more than one year out of training in this new, rapidly growing adult cardiac surgery program. Practice also encompasses adult thoracic and vascular. Beautiful midwest location on lake. Respond with curriculum vitae.

Please respond to Box 715. 715E/F

SITUATIONS WANTED

Cardiothoracic and vascular surgeon. Extensive experience. Wishes to relocate. Willing to assist or do surgery. Prefers Ventura, Oxnard, Santa Barbara, San Luis Obispo in southern California.

Please respond to Box 699. 699E/G

Young BC surgeon with recent one-year thoracic and vascular fellowship and laparoscopic skills wishes to relocate to solo/group practice situation. Extensive training in India and US. Excellent references.

Please respond to Box 703. 703E

Fifty-five-year-old peripheral vascular surgeon with busy Midwest practice would like to slow down and relocate to the West Coast. Has 18 years' experience with vein harvesting and assisting at cardiac and thoracic surgery. Seeks similar position with established cardiothoracic group.

Please call (219) 233-5191. 711E/H

Cardiac, thoracic, vascular surgeon, matured, extensive experience, looking for salaried position or assistant surgeon in cardiothoracic or vascular surgery. ABS, ABTS certified.

Please respond to Box 712. 712E

FELLOWSHIPS

Surgical residents/fellows—clinical residency/fellowship positions available in adult and pediatric cardiothoracic surgery. Large volume of cases. New Jersey license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart and Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015; (609) 893-6611, Ext 359. 653A/E

Cardiothoracic surgical fellowship—Allegheny General Hospital is seeking qualified candidates for a one-year, nonaccredited fellowship position in cardiothoracic surgery, available July 1, 1992, through June 30, 1993. The program enjoys a large volume of adult cardiac surgery and thoracic surgery cases, including thoracoscopy, esophageal and pulmonary resections, in addition to a strong research program. The program is assisted by seven physician assistants.

Please send CV and letters of recommendation to George J. Magovern, MD, Chairman, Department of Surgery, Allegheny General Hospital, 320 East North Ave, Pittsburgh, PA 15212; (412) 359-3715. 690D/G

Fellowship in congenital heart surgery available under the direction of Frank L. Hanley, MD. The position will involve a six-month clinical commitment with the option to extend the period to a full ytear. The optional time may be spent either in continued clinical training or as a research fellow in the cardiac surgery laboratory. Applicant qualifications must include completion of an accredited cardiothoracic surgery training program or present enrollment in such a program with at least one year of cardiothoracic experience. Openings are available for a starting date of July 1992 and at 6-month intervals following this.

Please direct all inquiries to Kristin Paxton, University of California, San Francisco, Division of Cardiothoracic Surgery, 505 Parnassus Ave, Box 0118, San Francisco, CA 94143; telephone: (415) 476-2606; Fax: (415) 476-9678. 697E

Fellowship, cardiothoracic surgery—immediate availability, for one year, nonapproved program. Excellent exposure and experience opportunity in cardiac surgery, as well as research. Ideal for an individual between general surgery residency and thoracic surgery residency. ABS eligible or certified. NYS licensure required or readily obtainable.

Please send CV to C. E. Anagnostopoulos, MD, Chief, Division of Cardiothoracic Surgery, c/o Marylee Davis, Human Resources, St. Luke's/Roosevelt Hospital Center, 114th St and Amsterdam Ave, NY, NY 10025; (212) 523-1611. EOE M/F. 707E

Information About Membership in The Society of Thoracic Surgeons

The Society of Thoracic Surgeons (STS) is the largest organization devoted primarily to the practice of thoracic and cardiovascular surgery. The major purpose of The Society is educational, with the aim of providing thoracic and cardiovascular surgeons from both academic and private practice environments a forum for presentation and discussion of scientific topics. As outlined in the original bylaws of The Society, this educational emphasis is designed to accomplish the broader goal of improving the quality and practice of thoracic and cardiovascular surgery as a specialty.

The STS recently held its 28th Annual Meeting. Since its founding in 1964, The Society has grown continually; the membership now includes the majority of board certified thoracic surgeons in the United States as well as thoracic and cardiovascular surgeons from 45 other countries.

In addition to holding an annual scientific meeting, the STS has more than 20 committees working on diverse matters related to improving thoracic and cardiovascular surgery as a specialty. Examples of these committees are: Standards and Ethics, Government Relations, Medico-Legal Affairs, Nomenclature and Coding, Education and Resources, Cardiothoracic Surgical Practice Guidelines, and Circulatory Support and Thoracic Transplantations. The Committee to Develop a National Database for Thoracic Surgery has implemented the first comprehensive database program for thoracic and cardiovascular surgeons in the United States; it is currently being offered to Society members.

There are five types of membership in The Society of Thoracic Surgeons: active, senior, honorary, international, and candidate.

Active Member Applicants for active membership must be surgeons whose practice is devoted primarily to the field of thoracic and cardiovascular surgery.

QUALIFICATIONS: Applicants must be Diplomates of the American Board of Thoracic Surgery or Fellows in The Royal College of Surgeons of Canada, and be established in the practice of thoracic and/or cardiovascular surgery for a minimum of 3 years. There must be sponsoring letters from three active STS members.

Senior Member Any active member or international member, upon reaching the age of 65 years, shall automatically become a Senior Member.

Honorary Member Honorary membership shall be reserved for distinguished persons worldwide who have achieved prominence in the field of thoracic and cardiovascular surgery and have contributed to its advancement. Honorary members shall be elected by a majority vote of The Society at its annual business session upon recommendation of the Council of the STS.

International Member Members from countries other than the United States and Canada were previously accepted only as active members. Because of differences in training and practice, the application process for foreign members was often complex and time consuming. To allow for greater international participation, the bylaws were revised to provide for the category of international member.

QUALIFICATIONS: Applicants shall reside outside the United States and Canada. They shall have completed training equivalent to that required for active membership. They shall have achieved appropriate certification or recognition of achievement in the specialty in their country and must devote the majority of their professional efforts to the interests of the specialty. Appropriate documentation of professional achievements shall be provided to the Membership Committee.

Candidate Member The candidate membership category was created to allow participation of younger surgeons not yet qualified for active membership.

QUALIFICATIONS: Applicants shall be enrolled in a thoracic and cardiovascular training program accredited by the Residency Review Committee for Thoracic Surgery under the authority of the Accreditation Council for Graduate Medical Education or in a training program similarly approved by The Royal College of Surgeons of Canada. Also, individuals who have completed their training in one of the above programs and are in process of acquiring certification or have been certified by the American Board of Thoracic Surgery or The Royal College of Surgeons of Canada and are awaiting fulfillment of the 3-year residence requirement for active membership are eligible for this type of membership.

If you would like to receive an application for membership in The Society, send the request printed below. This year's deadline for receipt of applications is September 1, 1992. We suggest you apply soon as it takes time to process the application. Approved applications will be presented to the membership at the January 1993 Annual Meeting in San Antonio, TX.

REQUEST FOR APPLICATIONS

Please send an application for: ☐ Active membership ☐ International membership ☐ Candidate membership

TO: NAME: ________________

ADDRESS: ________________

____

TELEPHONE NUMBER: ________________

Send to: Richard G. Sanderson, MD, Chairman, Membership Committee
The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611
Telephone: (312) 644-6610; FAX: (312) 527-6635

1993 Annual Meeting of The Society of Thoracic Surgeons

The Twenty-ninth Annual Meeting will be held at the San Antonio Convention Center in San Antonio, Texas, January 25–27, 1993.

APPLICATION FOR MEMBERSHIP

(Deadline: September 1, 1992)

Requests for application forms for membership in The Society of Thoracic Surgeons should be addressed to Richard G. Sanderson, MD, Chairman, Membership Committee, The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611.

The completed application forms and supporting letters must be in the hands of the Membership Committee by **September 1, 1992,** for the applicant to be considered for election at the meeting in January 1993.

CALL FOR ABSTRACTS

(Deadline: August 17, 1992)

Abstracts for papers to be presented at the 1993 Annual Meeting are now being accepted. The deadline for receipt of abstracts is **August 17, 1992.** No papers *received* after this date will be accepted for inclusion in this year's program. An original and one copy should be submitted, using the official Society abstract form (on verso of this page), to Adnan Cobanoglu, MD, Timothy J. Gardner, MD, and Thomas W. Shields, MD, Co-Chairmen, Program Committee (Abstracts), The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611. Additional forms are available upon request from The Society. Abstracts must summarize an original contribution not presented or accepted for presentation elsewhere. Abstracts must be in the hands of the Program Committee by **August 17, 1992.** It is requested that the covering letter indicate the author who is to receive notice of acceptance or rejection **and** the author who will present the paper.

Abstracts may also be submitted for consideration in the Poster Session held in the exhibit area. Authors will be responsible for developing the poster presentation. Guidelines will be furnished.

The Thoracic Surgery Directors Association (TSDA) has established a Resident Presentation Award. Potential TSDA Resident Award abstracts must represent original work by the resident, who is to be first author and presenter. TSDA Resident Award abstracts may be directed to the regular Scientific Session or the Research Forum.

Essayists are reminded that according to the bylaws of The Society, all papers accepted for presentation: (1) must be submitted in *triplicate* to the Secretary at the time of presentation or to the Editor of *The Annals of Thoracic Surgery* prior to presentation; and (2) become the property of The Society if they are accepted for presentation.

It is well recognized that abstracts frequently belie their content by virtue of poor organization, and as a result valuable contributions to the Scientific Sessions may be unrecognized. It is important that methods and results be clearly defined in the abstract; therefore, general statements such as "results will be presented" are not acceptable. When a procedure or method is stated to have "advantages," those advantages should be defined. Abstracts that simply summarize results without defining objectives and methods are equally undesirable.

Speakers for accepted papers are limited to ten minutes.

Instructions for Abstracts

The official abstract form printed on verso of this page and available from The Society, or photocopies thereof, must be used. **Authors must categorize the principal subject of their abstract by checking the appropriate box.**

If the abstract should also be submitted for the Poster Session, please check the additional appropriate box.

If the author wishes to submit the abstract for consideration for the Thoracic Surgery Directors Association Award competition, the *additional* appropriate box must be checked. Also, the name of the Program Director must appear on a TSDA Resident Award abstract.

1. Full names of authors must appear on the abstract.
2. Institution or address is to be given, but omit titles, degrees, and appointments.
3. Abstracts must be limited to 250 words and must be typed double-spaced.
4. When percentages are used, the absolute numbers of derivation must be stated.
5. The body of the abstract should include:
   a. A brief statement of the purpose of the study being presented, with reference to the current state of research in the field.
   b. The methods of study or experimental approach clearly, but briefly, defined.
   c. A summary of the results and/or conclusions of the study, including sufficient details to support those conclusions.
   d. A statement concerning the significance of the work and its possible implications for further research.
6. The form must be signed by the senior author attesting that the material will not be presented elsewhere if accepted for the scientific program nor published elsewhere if accepted for publication in *The Annals of Thoracic Surgery.*

In discussion of papers, The Society encourages a healthy spirit of constructive critical review and rebuttal by comments pertinent to the content of the paper being presented. Presentation of discussion in the form of "secondary papers" will not be welcomed.

CALL FOR SURGICAL FILMS OR VIDEO TAPES

(Deadline: August 3, 1992)

The popular Surgical Motion Picture program will again be presented at the Orlando meeting. The Program Committee hereby solicits the submission of surgical audiovisual presentations, which may portray a surgical procedure or simply a technical maneuver that the surgeon thinks will be of interest to The Society. The film (tape) may not exceed ten minutes in length. Sound is acceptable but not necessary; however, live narration by the principal surgeon is a requirement for participation in the movie night program. Presentations should be on 16-mm film, ¾-inch U-Matic video tape, or ½-inch VHS tape. The deadline for submission is **August 3, 1992.** Films and video tapes also should be sent to Adnan Cobanoglu, MD, Timothy J. Gardner, MD, and Thomas W. Shields, MD, Co-Chairmen, Program Committee, at The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611.

Richard P. Anderson, MD
Secretary

or Committee use only:

THE SOCIETY OF THORACIC SURGEONS

Abstract Form

LIMIT TO 250 WORDS AND DOUBLE-SPACE

For Committee use only:
Rating: (Highest 1)

1☐ 2☐ 3☐ 4☐ 5☐

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**EASE CHECK ONE
PROPRIATE
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Pulmonary
Esophagus
Chest wall
Mediastinum
Trauma
Transplantation
Heart
Great vessels
Valves
Congenital
Coronary
Electrophysiology
Myocardial protection
Extracorporeal circulation
Endoscopy
Vascular surgery
Research, Cardiac
Research, Congenital Cardiac
Research, Transplantation
Research, General Thoracic

PLEASE CHECK IF ALSO SUBMITTED FOR THE THORACIC SURGERY DIRECTORS ASSOCIATION AWARD

ogram Director's
ame:

I acknowledge that the material will not be presented elsewhere if accepted for presentation on The Society of Thoracic Surgeons Scientific Program. I further understand that the Editorial Board of *The Annals of Thoracic Surgery* has the right of first refusal for publication of this material.

Signature of Senior Author

NATIONAL UNIVERSITY OF SINGAPORE
DEPARTMENT OF SURGERY

Applications are invited for teaching appointments in the Department of Surgery. Candidates should possess an approved basic medical degree. In addition, he/she must possess one of the following: Board certificate in cardiothoracic surgery, FRCS or equivalent with experience in cardiothoracic surgery.

There are opportunities for active clinical practice in open heart, thoracic and vascular surgery with experimental surgical research and undergraduate and postgraduate teaching.

Gross annual emoluments range as follows:

Lecturer	S$53,160 - 64,200
Senior Lecturer	S$58,680 - 100,310
Associate Professor	S$88,650 - 122,870

(US$1.00 = S$1.63 approximately)

The commencing salary will depend on the candidate's qualifications, experience and the level of appointment offered. In addition, appointees who are regular appointments will receive a Specialist Allowance (SA) under the Professional Fee Scheme, the rates for which are as follows:

Lecturer	15% or 20% of gross salary
Senior Lecturer	25% or 40% of gross salary
Associate Professor	40% of gross salary

Senior Lecturers and Associate Professors who are designated Consultants may retain in full professional fees earned during the clinical sessions devoted to private patients which are over and above their SA up to twice their gross annual salary. For additional fees earned thereafter, part of the fees to be retained by the staff member will depend on his contribution to teaching, research and clinical service. Lecturers and Senior Lecturers designated as Senior Registrars may retain professional fees earned over and above their SA, up to 60% of their gross annual salary. The number of sessions for private patients will be limited to 4 out of 11 sessions in a week.

Staff on visiting appointments will be provided with emoluments comparable to those offered to staff on regular contracts.

Leave and medical benefits will be provided. Depending on the type of contract offered, other benefits may include: provident fund benefits or an end-of-contract gratuity, a settling-in allowance of S$1,000 or S$2,000, subsidised housing at normal rentals ranging from S$100 to S$216 p.m., education allowance for up to three children subject to a maximum of S$16,425 per annum per child, passage assistance and baggage allowance for the transportation of personal effects to Singapore.

Application forms and further information on terms and conditions of service, including the Professional Fee Scheme, may be obtained from:

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Personnel Department
National University of Singapore
10 Kent Ridge Crescent
Singapore 0511

The Director
North America Office
National University of Singapore
55 East 59th Street
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Tel: (212) 751-0331

Enquiries may also be sent through **BITNET** to: **PERSDEPT @ NUSVM**, or through **Telefax: (65) 7783948**

THE CLEVELAND CLINIC FOUNDATION
DEPARTMENT OF THORACIC AND CARDIOVASCULAR SURGERY
BOARD RESIDENCY POSITIONS AVAILABLE

Due to expanded program, additional Board Residency positions are available as follows:

First Year - July 1, 1992
Second Year - July 1, 1992

The Cleveland Clinic Foundation's Department of Thoracic and Cardiovascular Surgery performs 3,000 open heart operations annually with an increasing proportion of either complex procedures or reoperations. Active sections exist in all facets of adult cardiac surgery including: reparative valvular procedures, electrophysiological surgery, heart transplantation, myoplasty and circulatory support. The general thoracic surgery service includes all facets of general thoracic surgery with an extensive commitment to surgery of the esophagus and pulmonary transplantation. The service performs over 800 procedures yearly with 450 major operations. For information, please contact:

The Cleveland Clinic Foundation
Department of Thoracic and Cardiovascular Surgery
Desk F - 25
Education Coordinator, Laura L. Cotton
9500 Euclid Avenue
Cleveland, OH 44195
216-445-6816

THE CLEVELAND CLINIC FOUNDATION
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CLINICAL ASSOCIATE

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The Cleveland Clinic Foundation's Department of Cardiovascular Surgery performs 3000 open heart operations annually with an increasing proportion of either complex procedures or reoperations. Active sections exist in all facets of adult cardiac surgery including: reparative valvular procedures, electrophysiological surgery, heart transplantation, and circulatory support. For information please contact: **Robert W. Stewart, M.D.**

FELLOWSHIP IN GENERAL THORACIC SURGERY

A one year fellowship beginning July 1, 1993, is available for a board eligible or certified cardiothoracic surgeon seeking additional training in general thoracic surgery. This one year program includes all aspects of general thoracic surgery with an extensive commitment to surgery of the esophagus and pulmonary transplantation. The service performs over 800 procedures yearly with 450 major operations. For information please contact: **Thomas W. Rice, M.D.**

Cleveland Clinic Foundation
One Clinic Center
9500 Euclid Avenue
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Robert C. Parker, Jr., M.D.
Medical Director
Carle Clinic Association
602 West University, Urbana, Illinois 61801
call collect (217) 383-3399, FAX (217) 383-3163

Hospital of the University of Pennsylvania

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Verdi J. DiSesa, M.D.
Division of Cardiothoracic Surgery
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104
(215) 662-2022

Hospital of the University of Pennsylvania and Children's Hospital of Philadelphia

Fellowship in Adult and Pediatric Cardiothoracic Surgery

The Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia have an opening in a one year fellowship in adult and pediatric cardiothoracic surgery. Experience includes adult cardiac surgery, thoracic surgery, and pediatric cardiac surgery with active programs in adult and pediatric heart, heart-lung, and isolated lung transplantation. Pennsylvania license is required. Contact:

Verdi J. DiSesa, M.D.
Division of Cardiothoracic Surgery
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104
(215) 662-2022

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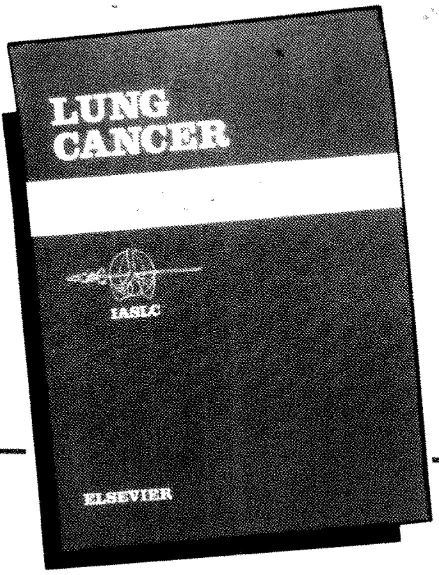

LUNG CANCER

Journal of the International Association for the Study of Lung Cancer

Lung Cancer aims to provide the members of the International Association for the Study of Lung Cancer (I.A.S.L.C.) and other individuals or organizations with the most recent information on lung cancer. The Journal publishes full-length articles of original research on clinical and basic science aspects of topics represented by the fields of interest of Lung Cancer (see below). Short communications, technical notes and reviews may also be published.
Each issue will also function as a forum for rapid exchange of information among members of the I.A.S.L.C. Lung Cancer contains up-to-date news from the I.A.S.L.C., reports from national and international groups working with lung cancer, book reviews and review articles, in which selected topics on lung cancer are discussed. In addition, each issue includes a reference section derived from the Excerpta Medica Database, with key abstracts covering the literature on lung cancer, classified under the following headings: (i) Prevention (ii) Epidemiology and etiology (iii) Basic biology (iv) Pathology (v) Clinical assessment (vi) Surgery (vii) Chemotherapy (viii) Radiotherapy (ix) Combined treatment modalities (x) Other treatment modalities (xi) Reviews (xii) Miscellaneous

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